Evidence Tables

Evidence Table 1. Nebulized Epinephrine vs. Nebulized Saline Placebo

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Comorbidities
Author Kristjansson et al., 1993[52] **Setting:** Sweden, Norway, multi-center, inpatient **Followup:** Acute **Study design** RCT-P **Length of enrollment** NR **Masking** Double-blind	To examine the effect of nebulized racemic adrenaline in infants and toddlers with acute bronchiolitis	**Inclusion criteria** • < 18 mos • No atopic eczema • Symptom score of 4 or more (0 - 10 scale) • Diagnosis of bronchiolitis according to the criteria of Court:[19] – rapid respiration, dyspnea, wheezing, chest recession, cough, rales, ronchi very frequent (present in 50% or more of children in age group) – visible chest distension, increased pulmonary translucency on chest radiograph, nasal discharge, red pharynx frequent (present in 25% - 50% of children in age group) – Fever very frequent, high fever uncommon • Symptom score of 4 or more (0 - 10 scale) **Exclusion criteria** None listed	**Number** 34 eligible, 29 completed study **Sex** Racemic adrenaline: 67% male (10/15) Placebo: 64% male (9/14) **Mean age at enrollment** NR **Mean gestational age** NR **Comorbidities** None

Evidence Table 1. Nebulized Epinephrine vs. Nebulized Saline Placebo (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 15)** Nebulized racemic adrenaline (20 mg/µl) 0.1 ml if < 5 kg 0.15 ml if 5 - 6.9 kg 0.2 ml if 7 - 9.9 kg 0.25 ml if >10 kg Mixed in 3 ml 0.9% saline, nebulized with air flow of 8 L/min via spacer and close fitting facemask **Group B (n = 14)** Nebulized placebo Identically appearing solution and schedule **Other treatment** NR	**Outcomes** Primary outcome • Mean symptom score at 0, 15, 30, 45, 60 mins after inhalation • Mean change in SaO_2 at 0, 15, 30, 45, 60 mins after inhalation **Secondary outcomes** • Mean change in $TcPo_2$ (kPa) at 0, 15, 30, 45, 60 mins after inhalation • Mean respiratory rate (breaths/min) at 0, 15, 30, 45, 60 mins after inhalation • Mean heart rate (beats/min) at 0, 15, 30, 45, 60 mins after inhalation • Mean diastolic and systolic pressure (mm Hg) at 0, 15, 30, 45, 60 mins after inhalation **Subgroup analysis** Severely affected infants with baseline SaO_2 < 93% (n = 11) **Adverse events** None other than circumoral paleness	**Significant differences between study groups** • Clinical score significantly lower in adrenaline group at all time intervals (P < 0.05) • SaO_2 improvement in adrenaline group significant (P < 0.05) immediately post-treatment but not thereafter • Significantly different at all time internals (P < 0.05) • No significant differences at 1 hr • No significant differences at 1 hr • No significant differences at 1 hr • SaO_2 significantly elevated throughout one hr period post-treatment (P < 0.05)	**Quality** Fair **Significant differences at baseline** SaO_2 and $TcPo_2$ lower in racemic adrenaline group, difference significant for $TcPo_2$ only (P < 0.05) **Other comments** • Adrenaline group had lower $TcPo_2$ but CIs have significant overlap • No statistical correction for multiple comparisons

Evidence Table 2. Subcutaneous Epinephrine vs. Saline Placebo

Study characteristics	Stated objective of study	Inclusion/exclusion criteria	Demographic Characteristics and Cormorbidities
Author Lowell et al., 1987[110] **Setting:** United States, ED **Followup:** Acute **Study design** RCT-P **Length of enrollment** October 1982-May 1983 **Masking** Double-blind	To evaluate the efficacy of subcutaneous epinephrine in improving respiratory distress in children under the age of 24 months with acute episodes of wheezing	**Inclusion criteria** • < 24 months of age • Wheezing on physical exam (high pitched, continuous, musical, respiratory sound on 2 examinations at least 5 mins. apart) **Exclusion criteria** • Prior bronchodilator therapy • Chronic cardorespiratory problem (cystic fibrosis or congenital heart disease) • Heart rate = 200 beats/min. • Respiratory rate = 100 breaths/min • Lethargy judged to be in incipient respiratory failure	**Number** 45 eligible, 30 randomized, 12 entered in observational cohort **Sex** Epinephrine: 63 % male (10/16) Placebo: 71% male (10/14) **Mean age at enrollment in mo. ± SD** Epinephrine: 8.9 ± 5.8 Placebo: 9.9 ± 5.6 **Mean gestational age** NR **Comorbidities** None

Evidence Table 2. Subcutaneous Epinephrine vs. Saline Placebo (continued)

Intervention	Outcome		Quality
Intervention **Group A (n=16)** Epinephrine 0.1 ml/kg (1 mg/ml) x 2 15 mins. apart **Group B (n=14)** Placebo Saline 0.01 ml/kg x 2 15 mins. apart **Other treatment** NR	**Outcomes** **Primary outcome** • Absolute change in clinical score (respiratory assessment change score or RACS) - Graphical presentation, figures cannot be extracted • Improvement, defined as RACS = 4 or RACS<4 (epinephrine vs. placebo) - 56% vs. 7% **Subgroup analysis** • Age - < 6 mo. - = 6 mo. to < 12 mo. - = 12 mo. to < 18 mo. - = 18 mo. to < 24 mo. **Adverse events** NR	**Significant differences between study groups** • *P* < 0.05 • *P* = 0.0067 • *P* values NR	**Quality** Good **Significant differences at baseline** None **Other comments** Observational cohort included to account for selection bias, observational cohort more likely to be moderately or severely ill (58%) compared to experimental cohort (30%)

Evidence Table 3. Nebulized Epinephrine vs. Nebulized Bronchodilators (Salbutamol or Albuterol)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Bertrand et al., 2001[53] **Setting** Chile, inpatient **Followup** Short term **Study design** RCT non-placebo **Length of enrollment** May to Sept 1994 **Masking** Double-blind	To compare the efficacy of multiple doses of epinephrine versus salbutamol in infants hospitalized with acute bronchiolitis	**Inclusion criteria** • < 1 yr of age • First wheezing episode • Acute onset of respiratory distress • X-ray of chest compatible with bronchiolitis **Exclusion criteria** • Prematurity • Chronic lung or cardiac disease • Lower respiratory tract infection within previous 3 mos • Bronchodilator or steroid therapy within the month	**Number** 33 enrolled, 30 completed study **Sex** Salbutamol: 50% male (7/14) Epinephrine: 56% male (9/16) **Mean age at enrollment (mo.± SE)** Salbutamol: 3.7 ± 0.6 Epinephrine: 3.9 ± 0.4 **Mean gestational age** NR **Comorbidities** None

Evidence Table 3. Nebulized Epinephrine vs. Nebulized Bronchodilators (Salbutamol or Albuterol) (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 14)** Salbutamol 0.5 ml (2.5 mg) plus 0.9% saline to total volume of 4 ml q 2 to 4 hrs **Group B (n = 53)** Epinephrine (1:1000) 0.5 ml (0.5 mg) plus 0.9% saline to total volume of 4 ml q 2 to 4 hrs Both salbutamol and epinephrine nebulized with continuous oxygen flow at 6 to 8 L/min via facemask **Other treatment** NR	**Outcomes**	**Significant differences between study groups**	**Quality** Good **Significant differences at baseline** None **Other comments** • The scores of 3 enrolled patients who were transferred to receive mechanical ventilation were excluded from the final analysis • Two of the significant outcomes (hospital - ization on Days 4 and 5) may be influenced by the larger number of adverse events in salbutamol group • Did not use intent to treat analysis
	Primary outcome • Mean duration of hospitalization in days ± SE (salbutamol vs. epinephrine): - 5.2 ± 1.0 vs. 4.1 ± 1.1 • Change in clinical scores pre and post treatment (at baseline, 24 and 36 hrs)	• No (P = 0.11) • Significant only for epinephrine at baseline (P = 0.025)	
	Secondary outcomes • Hospitalization on Day 4 (salbutamol vs. epinephrine) • Hospitalization on Day 5 (salbutamol vs. epinephrine) • Readmission within 2 wks • Mean length of O_2 treatment in days • Average % of O_2 required to maintain O_2 saturation > 94%	• Yes (P = 0.03) • Yes (P = 0.025) • No • No • No	
	Subgroup analysis None		
	Adverse events • Increase in heart rate on second day (mean heart rate ± SE),: - Salbutamol: 146 ± 4 - Epinephrine: 153 ± 2.9 • Development of atelectasis - Salbutamol: 3/14 - Epinephrine: 0/16 • Bacterial super - infection - Salbutamol: 2/14 - Epinephrine: 0/13	• P = 0.02	

Evidence Table 3. Nebulized Epinephrine vs. Nebulized Bronchodilators (Salbutamol or Albuterol) (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Menon et al., 1995[22] **Setting** Canada, Emergency department **Followup** • Acute • Short term **Study Design** RCT non-placebo **Length of enrollment** Jan 1994 - March 1994 **Masking** Double-blind	To compare the efficacy of epinephrine with that of salbutamol in outpatients with acute bronchiolitis	**Inclusion criteria** • 6 wks to 1 yr • O_2 saturation $\geq$ 85% and $\leq$ 96% • RDAI score $\geq$ 4 • First episode of wheezing • Clinical symptoms of viral respiratory infection (temperature $\geq$ 38°C or coryza) **Exclusion criteria** • Chronic cardiac or pulmonary disease • Diagnosis of asthma by a physician • Any previous use of bronchodilators • Severe disease requiring resuscitation or heart rate < 200 beats/min • Received glucocorticoids within the previous 24 hrs	**Number** 41 completed study **Sex** NR **Mean age (yrs ± SD)** Salbutamol: 0.4 ± 0.2 Epinephrine: 0.5 ± 0.2 **Mean gestational age** NR **Comorbidities** None

Evidence Table 3. Nebulized Epinephrine vs. Nebulized Bronchodilators (Salbutamol or Albuterol) (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 21)** Salbutamol 0.3 ml of a 5 mg/ml solution (1.5 mg) combined with 2.7 ml of 0.9 % saline at 0 and 30 mins **Group B (n = 20)** Epinephrine 3 ml of 1:1000 solution at 0 and 30 mins nebulized with continuous flow of O_2 at 5 to 6 L/min **Other interventions** Higher concentration of O_2 or extra doses of salbutamol as needed	**Outcomes**	**Significant difference between groups**	**Quality** Good **Significant differences at baseline** None reported **Other comments** None
	Primary Outcomes		
	• O_2 saturation at 30, 60 and 90 mins (salbutamol vs. epinephrine) - 60 mins: 94% vs. 96%	• Yes, at 60 mins (P = 0.02)	
	Secondary Outcomes		
	• Clinical scores at 30, 60 and 90 mins	• No (P values NR)	
	• Respiratory rate (breaths/min) at 30, 60, 90 mins	• No (P values NR)	
	• Heart rate (beats/min ± SD) at 30, 60 and 90 mins (salbutamol vs. epinephrine) - 90 mins: 165 ± 13 vs. 151 ± 16	• Yes, at 90 mins (P = 0.003)	
	• Hospitalization (salbutamol vs. epinephrine) - 81% (17/21) vs. 33% (7/20)	• Yes (P = 0.003)	
	• Mean duration of admission	• No (P = 0.4)	
	• Rate of discharge from ED in first 4 hrs	• Yes, faster for epinephrine group (P = 0.02 for survival analysis)	
	• Return visits to hospital within 24 hrs of hospital discharge	• No (P = 0.94),	
	Other analysis Effect of time, group, and interaction between time and group on outcomes based on repeated measures analysis		
	Adverse events Higher incidence of pallor in epinephrine group at 30 and 60 mins, diminished by 90 mins	• P = 0.01 at 30 mins P = 0.06 at 60 mins P = 0.13 at 90 mins	

Evidence Table 3. Nebulized Epinephrine vs. Nebulized Bronchodilators (Salbutamol or Albuterol) (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Reijonen et al., 1995[54] **Setting** Finland, Emergency room **Followup** Acute **Study design** RCT-P **Length of enrollment** Jan 1992 to Nov 1993 **Masking** Double-blind	To determine whether early treatment with nebulized racemic epinephrine improves RDAI score in infants with acute bronchiolitis	**Inclusion criteria** • Hospitalized patients age 1 - 23 mons • Clinical criteria of acute bronchiolitis: wheezing and respiratory distress in patient with acute URTI **Exclusion criteria** • Chronic cardiorespiratory disease (asthma, BPD, CHD) • Use of oral, nebulized or parenteral bronchodilator in preceding 6 hrs • Impending respiratory failure • If admitted at night (10 pm to 7 am)	**Number** 100 enrolled **Sex** REP[1]: 58% male (14/24) AP: 59% male (16/27) PRE: 79% male (19/24) PA: 84% male (21/25) **Mean age at enrollment (mo).± SD)** REP: 10.6 ± 5.6 AP: 9.9 ± 5.5 PRE: 10.1 ± 5.7 PA: 10.3 ± 7.5 **Mean gestational age** NR **Comorbidities** • 13% with previous history of wheezing (no sig diffs among groups) • 31% with atopy (no sig diffs among groups)

[1] REP: Racemic epinephrine followed by placebo
AP: Nebulized albuterol followed by placebo
PRE: Placebo followed by nebulized racemic epinephrine
PA: Placebo followed by nebulized albuterol

Evidence Table 3. Nebulized Epinephrine vs. Nebulized Bronchodilators (Salbutamol or Albuterol) (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 24)** REP Racemic epinephrine: 0.9 mg/kg in 2 ml saline Placebo: 0.9% saline **Group B (n = 27)** AP Albuterol: 0.15 mg/kg in 2 ml saline solution Placebo: 0.9% saline **Group C (n = 24)** PRE Same as REP **Group D (n = 24)** PA Same as AP All groups received 2 nebs 30 mins apart via nebulizer with continuous oxygen flow of 5 L/min **Other treatment** • O_2 as needed • IM epinephrine for all patients 60 mins after first inhalation	**Outcomes** **Primary outcomes** • Change in RDAI score - all groups showed improvement • Respiratory rates at 0, 15, 30, 45, 60, 75, 90 mins • SaO_2 at 0, 15, 30, 45, 60, 75, 90 mins • O_2 treatment • Heart rate at 0, 15, 30, 45, 60, 75, 90 mins **Subgroup analyses** • Age - <1 yr - >1 yr • Severity of disease - RDAI > 8 - RDAI = 8 **Adverse events** None observed	**Significant differences between study groups** • No • No • No • NR • No • No • No	**Quality** Good **Significant differences at baseline** None **Other comments** • Percentage of children with history of atopy high • All children admitted to ER care (and enrolled in subsequent study)[75]

Evidence Table 3. Nebulized Epinephrine vs. Nebulized Bronchodilators (Salbutamol or Albuterol) (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Sanchez et al., 1993[55] **Setting** Canada, Inpatient **Followup** Acute **Study design** RCT-C **Length of enrollment** Dec 1991 to Apr 1992 **Masking** Double-blind	To compare inhaled racemic epinephrine vs. salbutamol to test the efficacy of a combined a - and ß - receptor agonist in acute bronchiolitis	**Inclusion criteria** • <1 yr of age • acute bronchiolitis **Exclusion criteria** • Previous bronchodilator treatment prior to admit • History of: - wheezing - chronic cardiorespiratory disease (asthma, CF, BPD, CHD) - parental history of asthma	**Number** 32 enrolled, 24 completed study **Sex** 50% male (12/24) **Mean age at enrollment (mo ± SD)** 4.6 ± 0.5 **Mean gestational age** Not reported **Comorbidities** None

Evidence Table 3. Nebulized Epinephrine vs. Nebulized Bronchodilators (Salbutamol or Albuterol) (continued)

Intervention	Outcome		Quality
Interventions (n = 24) Infants sedated with oral chloral hydrate (80 mg/kg first dose) After 1 hr, infants received either salbutamol (0.03 ml/kg in 2 ml in 0.9% saline) or racemic epinephrine (0.1 ml/kg in 2 ml in 0.9% saline) 2.5 hrs later, a second dose of chloral hydrate (40 mg/kg) followed in 30 mins by the drug not previously given **Other treatment** Supplemental oxygen as needed	**Outcomes** **Primary Outcomes** • Respiratory rate (mean values before vs. after ± SD) - Salbutamol 47.0 ± 1.5 vs. 40.8 ± 0.8 - Racemic epinephrine 46.5 ± 1.4 vs. 35.5 ± 0.4 • SaO_2 (mean values before vs. after ± SD) - Salbutamol 91.5 ± 0.7 vs. 92.1 ± 0.7 - Racemic epinephrine 91.8 ± 0.8 vs. 93.0 ± 0.7 **Secondary Outcomes** Pulmonary function tests: • V_T • Heart rate • Minute ventilation • C_{DYN} - total • Resistance - inspiratory • Resistance - expiratory • Ti/Ttot **Adverse events** None observed	**Significant differences between study groups** • Not significant before treatment (*P* value NR), significant after treatment ($P < 0.001$) • Not significant before or after treatment (*P* value NR) • Not significant before or after treatment • Not significant before or after treatment • Not significant before treatment, significantly lower after epinephrine than after salbutamol • Not significant before or after treatment • Not significant before treatment, significantly lower after epinephrine than after salbutamol • Not significant before treatment, significantly lower after epinephrine than after salbutamol • Not significant before or after treatment	**Quality** Fair **Significant differences at baseline** None reported **Comments** • Limited generaliz-ability due to selection of infants with mild to moderate bronchiolitis, sedation of infants with chloral hydrate • Did not examine role of rebound after racemic epinephrine

Evidence Table 4. Nebulized Bronchodilators (Salbutamol or Albuterol) vs. Oral Bronchodilators, Nebulized Ipratropium Bromide, or Saline Placebo or No Treatment

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Can et al., 1998[24] **Setting** Turkey, emergency department **Followup** Acute **Study Design** RCT-P **Length of enrollment** Jan 1994 - Jan 1996 **Masking** Double-blind	To evaluate the efficacy and safety of salbutamol in infants with acute bronchiolitis	**Inclusion criteria** Derived from study by Wohl et al. 1990,[109] details not provided **Exclusion criteria** • < 24 mons • Prematurity and mechanical ventilation after birth • Chronic cardiopulmonary disease • Previous bronchodilator and steroid administration during the admission • Symptoms > 1 wk • Heart rate > 200 beats/min and/or respiratory rate > 80 breaths/min • Lethargy or stupor • History of previous attack • Respiratory Distress Score < 5	**Number** 158 enrolled, 156 completed study **Sex** Salbutamol: 48% male Saline: 76% male Mist: 51% male **Mean age at enrollment (mo ± SD)** Salbutamol: 7.2 ± 4.2 Saline: 6.8 ± 2.1 Mist: 7.4 ± 5.3 **Mean gestational age** NR **Comorbidities** None

Evidence Table 4. Nebulized Bronchodilators (Salbutamol or Albuterol) vs. Oral Bronchodilators, Nebulized Ipratropium Bromide, or Saline Placebo or No Treatment (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 52)** Nebulized salbutamol 0.15 mg/kg in 2 ml saline **Group B (n = 52)** Nebulized saline **Group C (n = 52)** Mist in a tent In all groups, second dose given at 30 mins if RDS > 5 **Other treatment** Humidified O_2 at 5 L/min given to all groups	**Outcomes** **Primary Outcomes** • Mean RDS ± SD (salbutamol vs. saline vs. mist) - Initial: 11.0 ± 3.2 vs. 11.3 ± 3.6 vs. 10.8 ± 33 (33 quoted from text) - 30 mins.: 7.0 ± 3.1 vs. 9.7 ± 3.7 vs. 10.8 ± 3.6 - 60 mins.: 5.2 ± 1.8 vs. 10.2 ± 3.5 vs. 9.6 ± 3.4 • Percent with RDS> 5 at 30 mins (salbutamol vs. saline vs. mist) - 28% vs. 3% vs. 11% **Secondary Outcomes** • SaO_2 changes • Heart rate **Subgroup analysis** • Age - < 6 mo. vs. > 6 mo. **Adverse events** Frequency of tachycardia and hypoxia did not reach statistical significance, no details provided	**Significant differences between study groups** - No ($P > 0.05$) - $P < 0.0001$ for both salbutamol vs. saline and salbutamol vs. mist. Saline vs. mist not significant - $P < 0.0001$ for both salbutamol vs. saline and salbutamol vs. mist. Saline vs. mist not significant • P - value NR • Salbutamol lower, but not statistically significant • No • No	**Quality** Fair **Significant differences at baseline** • Group A had CXR findings consistent with acute bronchiolitis significantly more often ($P < 0.05$) than groups B and C **Other comments** • Followup limited to 60 mins • "Mist" not defined

Evidence Table 4. Nebulized Bronchodilators (Salbutamol or Albuterol) vs. Oral Bronchodilators, Nebulized Ipratropium Bromide, or Saline Placebo or No Treatment (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Cengizlier et al., 1997[58] **Setting** Turkey, Inpatient **Followup** • Acute • Short term **Study design** RCT non-placebo **Length of enrollment** NR **Masking** Cannot be determined	To evaluate the efficacy of oral or MDI salbutamol using a coffee cup as a spacer device in bronchiolitis	**Inclusion criteria** • First episode of bronchiolitis • 6 to 24 mons • Bronchiolitis diagnosed by ward pediatrician as expiratory wheezing of acute onset with signs of viral illness **Exclusion criteria** • Asthma • Cystic fibrosis • Congenital heart disease	**Number** 31 completed study **Sex** Oral salbutamol: 55% male (6/11) Inhaled salbutamol: 58% male (7/12) Control: 38% male (3/8) **Mean age at enrollment in mo. ± SD** Oral salbutamol: 9.6 ± 6.4 Inhaled salbutamol: 11.6 ± 1.2 Control: 9.2 ± 3.6 **Mean gestational age** NR **Comorbidities** None

Evidence Table 4. Nebulized Bronchodilators (Salbutamol or Albuterol) vs. Oral Bronchodilators, Nebulized Ipratropium Bromide, or Saline Placebo or No Treatment (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 11)** Oral salbutamol 0.1 mg/kg/dose QID **Group B (n = 12)** Inhaled salbutamol 200 µg/dose every 3° using an inhaler with a coffee cup as a spacer device **Group C (n = 8)** Control No therapy **Other treatment** Routine supportive care	**Outcomes** **Primary outcome** • Mean duration of hospitalization in days - oral salbutamol: 5 - inhaled salbutamol: 6 - control: 5 • Mean change in clinical scores between admission and discharge ± SD - oral salbutamol: 1.9 ± 0.4 - inhaled salbutamol: 2.0 ± 0.2 - control: 1.8 ± 0.3 **Secondary outcomes** • Increase in heart rate 1 hr after first dose of bronchodilator **Subgroup analysis** None **Adverse events** NR	**Significant differences between study groups** • No ($P > 0.05$ for both oral salbutamol vs. control and inhaled salbutamol vs. control) • No ($P > 0.05$ for both oral salbutamol vs. control and inhaled salbutamol vs. control) • No	**Quality** Fair **Significant differences at baseline** None: *P* values not provided, but groups do not appear to be significantly different **Other comments** None

Evidence Table 4. Nebulized Bronchodilators (Salbutamol or Albuterol) vs. Oral Bronchodilators, Nebulized Ipratropium Bromide, or Saline Placebo or No Treatment (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Dobson et al., 1998[37] **Setting** United States, inpatient **Followup** Short term **Study design** RCT-P **Length of enrollment** Dec 1995 - March 1996 **Masking** Double-blind	To determine whether albuterol enhances clinical and physiological recovery in hospitalized infants with moderately severe bronchiolitis	**Inclusion criteria** • < 24 months of age • First episode of wheezing during bronchiolitis season • Moderately severe bronchiolitis defined by the presence of one of the following - SaO_2 < 94% - moderate to severe accessory muscle use (= 2) or moderate to severe wheezing (= 2) **Exclusion criteria** • Underlying chronic cardiac or pulmonary disease • Significant concurrent illness (sepsis, meningitis, pneumonia, urinary tract infections, gastroenteritis) • Current gestational age <38 wks • History of wheezing requiring hospitalization or bronchodilator therapy before current illness • Concurrent steroid treatment • Severe bronchiolitis requiring intensive care (mechanical ventilation, documented apnea, heart rate > 200 beats/min, hypercarbia)	**Number** 58 enrolled, 52 completed study **Sex** Albuterol: 61% male (14/23) Placebo: 45% male (13/29) **Mean age at enrollment (mo.± SD)** Albuterol: 5.1 ± 3.7 Placebo: 6.1 ± 5.4 **Mean gestational age (wks. ± SD)** Albuterol: 39.2 ± 1.6 Placebo: 38.8 ± 2.4 **Comorbidities** None reported

Evidence Table 4. Nebulized Bronchodilators (Salbutamol or Albuterol) vs. Oral Bronchodilators, Nebulized Ipratropium Bromide, or Saline Placebo or No Treatment (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 23)** Nebulized albuterol Dose: 1.25 mg if <10 kg, 2.5 mg if >10 mg q. 2 hr x 24 hos then q. 4 hr x 48 hrs **Group B (n = 29)** Placebo 3ml normal saline by nebulized aerosol following same dosing schedule **Other treatment** Routine supportive care as needed	**Outcomes** **Primary Outcomes** • Improvement in % SaO_2 on room air over time for albuterol vs. placebo (95% CI) - 0 - 24 hrs: 1.8% (0.1% - 3.6%) vs. 1.6% (0.2% - 3.0%) - 24 hrs to max SaO_2: 2.2% (1.3% - 3.1%) vs. 1.8% (0.9% - 2.8%) - Time 0 to max SaO_2: 4.0% (2.6% - 5.4%) vs. 3.4% (2.4% - 4.5%) **Secondary Outcomes** • Percent patients discharged from hospital at 24, 48, 72 hrs • Length of hospital stay **Subgroup analysis** • Age - <12 mons of age **Adverse events** "Comparison of adverse events for albuterol vs. control groups approaches, but does not reach, statistical significance" (no details provided)	**Significant differences between study groups** • No • No • No	**Quality** Good **Significant differences at baseline** None **Other comments** Had 90% power to detect change in SaO_2 of = 2%

Evidence Table 4. Nebulized Bronchodilators (Salbutamol or Albuterol) vs. Oral Bronchodilators, Nebulized Ipratropium Bromide, or Saline Placebo or No Treatment (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Gadomski et al., 1994[60] **Setting** Egypt, outpatient and emergency room **Followup** Acute **Study Design** RCT-P, Group E not randomized **Length of enrollment** NR **Masking** Double-blind	• To determine the efficacy of albuterol in reducing respiratory distress in infants with bronchiolitis • To assess effectiveness of route of delivery (nebulization vs. oral) • To determine the incidence of positive blood culture among first-time wheezing infants	**Inclusion criteria** • <18 mons • First episode of wheezing • Recurrent wheezers/asthmatics recruited as open-label control subjects **Exclusion criteria** • Chronic diseases of the cardiorespiratory system • Heart rate > 200 beats/min • Cyanosis • Apathy, lethargy, or an otherwise depressed sensorium suggestive of incipient respiratory failure or sepsis • Persistent vomiting • Refused feedings	**Number** Number enrolled not stated, 128 randomized and 41 enrolled in study of recurrent wheezing, 169 completed study **Sex** Nebulized albuterol: 75% male Nebulized saline: 72% male Oral albuterol: 69% male Oral saline: 75% male Recurrent wheezers: 63% male **Median age at enrollment** Nebulized albuterol: 4.0 mos Nebulized saline: 5.0 mos Oral albuterol: 5.5 mos Oral saline: 4.0 mos Recurrent wheezers: 12.0 mos **Mean gestational age** NR **Comorbidities** None reported

Evidence Table 4. Nebulized Bronchodilators (Salbutamol or Albuterol) vs. Oral Bronchodilators, Nebulized Ipratropium Bromide, or Saline Placebo or No Treatment (continued)

Intervention	Outcome		Quality
Intervention	**Outcomes**	**Significant differences between study groups**	**Quality**
Group A (n = 32) Nebulized albuterol 0.15 mg/kg x 2 doses 30 mins. apart **Group B (n = 32)** Nebulized saline 0.9% solution x 2 doses 30 mins apart All doses delivered via nebulizer with pediatric face mask with room air at flow rate of 4 - 6 L/min **Group C (n = 32)** Oral albuterol 0.15 mg/kg PO **Group D (n = 32)** Oral rehydration solution (with similar color and odor as Group C) **Group E (n = 41)** Recurrent wheezers treated with nebulized albuterol 0.15 mg/kg x 2 or 3 doses **Other treatment** After 60 mins, open-label albuterol nebulization treatment given to infants whose clinical condition had worsened or not improved prior to breaking randomization code	**Primary Outcomes** • Clinical scores at baseline, 30 and 60 mins • Respiratory rates at baseline, 30 and 60 mins • Heart rates at baseline, 30 and 60 mins • Oxygen saturation at baseline, 30 and 60 mins **Secondary Outcomes** • Leukocyte counts • Antimicrobial activity in urine • Blood culture • Chest x-rays **Subgroup analysis** Change in state (i.e., falling asleep, waking up) **Adverse events** NR	• No • No • No • No • No • No • No • No • No	**Significant differences at baseline** Recurrent wheezers older, heavier, more likely to have received meds before visit **Other comments** Group E not randomized

Evidence Table 4. Nebulized Bronchodilators (Salbutamol or Albuterol) vs. Oral Bronchodilators, Nebulized Ipratropium Bromide, or Saline Placebo or No Treatment (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Gadomski et al., 1994[59] **Setting** United States, Emergency department and outpatient clinic **Followup** Acute **Study design** RCT-P **Length of enrollment** Feb 1990 – Dec 1992 **Masking** Double-blind	To examine the efficacy of albuterol (oral and nebulized) in the management of bronchiolitis	**Inclusion criteria** • 15 months of age • First episode of wheezing • Clinical definition of bronchiolitis: - acute infection of lower respiratory tract - fever - rhinitis - tachypnea - expiratory wheezing - increased respiratory effort **Exclusion criteria** • Previous use of bronchodilator • History of intubation and mechanical ventilation • Chronic cardiorespiratory diseases (congenital heart disease, CF, BPD) • Severely ill infants: - heart rate > 200 beats - respiratory rate > 100 breaths/min - apathy/lethargy - depressed sensorium suggestive of incipient respiratory failure or sepsis	**Number** 93 randomized, 5 withdrawn, 13 in pilot study and did not complete protocol, 76 completed both assessments **Sex** Nebulized albuterol: 45% male (10/22) Nebulized saline: 57% male (13/23) Oral albuterol: 58% male (11/19) Oral placebo: 63% male (15/24) **Mean age at enrollment (mo)** Nebulized albuterol: 5.6 Nebulized saline: 5.8 Oral albuterol: 4.8 Oral placebo: 5.3 **Mean gestational age** NR **Comorbidities** None

Evidence Table 4. Nebulized Bronchodilators (Salbutamol or Albuterol) vs. Oral Bronchodilators, Nebulized Ipratropium Bromide, or Saline Placebo or No Treatment (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 22)** Nebulized albuterol If = 7 kg, 1 mg/dose nebulized albuterol in 3 mL saline x 2 doses, 30 mins apart If > 7 kg, 0.15 mg/kg/dose nebulized albuterol in 3 mL x 2, 30 mins apart Nebulized with compressed air at 6 L/min with pediatric face mask **Group B (n = 23)** Nebulized saline 3 mL saline x 2, 30 mins apart **Group C (n = 19)** Oral albuterol If = 7 kg, 2.5 mL (1 mg) If > 7 kg, 0.15 mg/kg/dose **Group D (n = 24)** Oral placebo Oral rehydration solution, same color as oral bronchodilator	**Outcomes** **Primary outcome** • Respiratory rate at baseline, 30 and 60 mins • Change in respiratory rate between baseline and 30 mins and baseline and 60 mins **Secondary outcomes** • Clinical score at baseline, 30 and 60 mins • Change in clinical score between baseline and 30 mins and baseline and 60 mins • Oxygen saturation at baseline, 30 and 60 mins • Change in oxygen saturation between baseline and 30 mins and baseline and 60 mins • Heart rate at baseline, 30 and 60 mins • Change in heart rate between baseline and 30 mins and baseline and 60 mins • Need for additional treatment • Number hospitalized **Subgroup analysis** • Age - < 6 mo vs. = 6 mo. • Change in state	**Significant differences between study groups** • No • No • No • No • No • No • Yes (heart rate significantly higher for oral albuterol group at 60 mins, *P* = 0.006) • Yes (change in heart rate significantly higher for oral albuterol group at 60 mins, *P* = 0.008) • No • No • No • Yes (*P* = 0.01 for change in RR and change in clinical score)	**Quality** Good **Significant differences at baseline** None **Other comments** Oral placebo same color as active drug, but no attempt made to mask flavor of albuterol itself

Evidence Table 4. Nebulized Bronchodilators (Salbutamol or Albuterol) vs. Oral Bronchodilators, Nebulized Ipratropium Bromide, or Saline Placebo or No Treatment (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Gadomski et al., 1994[59] (continued)			

Evidence Table 4. Nebulized Bronchodilators (Salbutamol or Albuterol) vs. Oral Bronchodilators, Nebulized Ipratropium Bromide, or Saline Placebo or No Treatment (continued)

Intervention	Outcome	Quality
Other treatment After 60 mins, open-label albuterol nebulization treatment given to infants whose clinical condition had worsened or not improved prior to breaking randomization code	**Adverse events** • Increased heart rate among oral albuterol group • Facial flushing at 60 mins (3 nebulized albuterol subjects, 1 oral albuterol subject) • Hyperactivity (2 nebulized albuterol subjects, 1 oral albuterol subject) • Coughing (1 nebulized saline subject, 1 oral placebo subject) • Tremor at 60 mins (1 oral albuterol subject)	

Evidence Table 4. Nebulized Bronchodilators (Salbutamol or Albuterol) vs. Oral Bronchodilators, Nebulized Ipratropium Bromide, or Saline Placebo or No Treatment (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Goh et al., 1997[61] **Setting** Singapore, Inpatient **Followup** Acute **Study design** Placebo, salbutamol and ipratropium bromide: RCT-P Humidified oxygen: open label **Length of enrollment** Placebo, salbutamol and ipratropium bromide: Aug 1992 to Jul 1993 Humidified oxygen: Nov 1993 to Apr 1994 **Masking** Attending physician blinded, not clear if caretakers were blinded	To determine the efficacy of bronchodilators in the treatment of bronchiolitis	**Inclusion criteria** • < 2 yrs old • Admitted for signs and symptoms of bronchiolitis **Exclusion criteria** • Congenital heart disease • Immunocompromised patients • Recurring mechanical ventilation • History of previous wheeze	**Number** Between Aug 1992 and Jul 1993, 99 patients randomized, 89 completed study Between Nov 1993 and Apr 1994, 21 patients included **Sex** Placebo: 69% male (20/29) Salbutamol: 80% male (24/30) Ipratropium bromide: 67% male (20/30) Humidified oxygen 73% male (22/30) **Mean age at enrollment (mo ± SD)** Placebo: 7.4 ± 0.89 Salbutamol: 5.7 ± 0.77 Ipratropium bromide: 5.2 ± 0.67 Humidified oxygen: 5.9 ± 0.71 **Mean gestational age** NR **Comorbidities** None

Evidence Table 4. Nebulized Bronchodilators (Salbutamol or Albuterol) vs. Oral Bronchodilators, Nebulized Ipratropium Bromide, or Saline Placebo or No Treatment (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 29)** Nebulized normal saline 2 ml **Group B (n = 30)** Nebulized salbutamol 2.5 mg/mL If = 6 mo., 0.3 mL made up to 2 mL with normal saline If > 6 mo., 0.6 mL made up to 2 mL with normal saline **Group C (n = 30)** Nebulized ipratropium bromide 250 µg/mL made up to to 2 ml saline by age as above All nebulizations over 10 to 15 mins by face mask driven by oxygen flow at flow rate of 6 to 8 L/min **Group D (n = 31)** Humidified oxygen **Other treatment** As indicated	**Outcomes** **Primary outcome** • Mean duration of hospitalization in days for all groups: - 4 (no other details provided) **Secondary outcomes** • Severity scores at baseline, Day 1, Day 2 and Day 3 **Subgroup analysis** • Duration of hospitalization by age • Age > 6 mo vs. age < 6 mo - Hospitalization days - Number of nebulizations **Adverse events** NR	**Significant differences between study groups** • No ($P > 0.05$) • No ($P > 0.05$) • No ($P > 0.05$) • No ($P > 0.05$)	**Quality** Fair **Significant differences at baseline** None **Other comments** Humidified oxygen group was enrolled 1 yr after the RCT portion of the study, not randomized

Evidence Table 4. Nebulized Bronchodilators (Salbutamol or Albuterol) vs. Oral Bronchodilators, Nebulized Ipratropium Bromide or Saline Placebo or No Treatment

Study characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Hickey et al., 1994[57] **Setting:** United States, Emergency Department **Followup:** Acute **Study design** RCT-C **Length of enrollment** Dec 1989 to Feb 1990, Nov 1990 to March 1991 **Masking** Double-blind	To determine the efficacy of albuterol delivered via metered-dose inhaler with spacer for the treatment of wheezing infants	**Inclusion criteria** • 1-18 months • Wheezing **Exclusion criteria** • Cardiac or musculoskeletal disease • History of treatment with supplemental oxygen • Bronchodilator use in the previous 24 hrs • Severe respiratory distress (very poor air entry, cynanosis or fatigue)	**Number** 47 eligible, 42 enrolled **Sex** Group 1: 74% male (14/19) Group 2: 61% male (14/23) **Median age at enrollment in mo (range)** Group 1: 6.2 (1.2-18.3) Group 2: 7.0 (2.3-18) **Mean gestational age** NR **Comorbidities** None

Evidence Table 4: Nebulized Bronchodilators (Salbutamol or Albuterol) vs. Oral Bronchodilators, Nebulized Ipratropium Bromide or Saline Placebo or No Treatment (continued)

Intervention	Outcome		Quality
Intervention **Group A (n=19)** 2 treatments of albuterol followed by 2 treatments of placebo **Group B (n=23)** 2 treatments of placebo followed by 2 treatments of albuterol 2 puffs per treatment, either 90 µg of albuterol per puff or only the oleic acide dispersant. 20 mins. interval between treatments, delivered via metered-dose inhaler and "home-made" spacer device crafted at the Children's Hospital of Pittsburgh **Other treatment** NR	**Outcomes** **Primary outcome** • Improvement in wheezing scores – Graphical presentation, figures cannot be extracted • Improvement in retraction scores – Graphical presentation, figures cannot be extracted • Mean respiratory rate at baseline, 40 mins and 80 mins • Mean heart rate at baseline, 40 mins and 80 mins • Mean oxygen saturation at baseline, 40 mins and 80 mins	**Significant differences between study groups** • No sig. diffs. between groups, however Group A scores improved significantly from baseline by 2nd treatment ($P < 0.05$), Group B scores improved significantly only by 4th treatment ($P < 0.05$) • No sig. diffs. between groups, however Group A scores did not improved significantly from baseline, Group B scores improved significantly by 4th treatment ($P < 0.05$) • No diffs between groups at any time, no significant improvement within group over time • No diffs between groups at any time, no significant improvement within group over time • No diffs between groups at any time, no significant improvement within group over time	**Quality** Good **Significant differences at baseline** None **Other comments** None

Evidence Table 4: Nebulized Bronchodilators (Salbutamol or Albuterol) vs. Oral Bronchodilators, Nebulized Ipratropium Bromide or Saline Placebo or No Treatment (continued)

Study characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Hickey et al., 1994[57] (continued)			

Evidence Table 4. Nebulized Bronchodilators (Salbutamol or Albuterol) vs. Oral Bronchodilators, Nebulized Ipratropium Bromide or Saline Placebo or No Treatment (continued)

Intervention	Outcome		Quality
	Subgroup analysis • First episode of wheezing • RSV status	• Retraction scores lower for albuterol for first wheezers and RSV positive ($P < 0.05$), no other significant outcomes	
	Adverse events NR		

Evidence Table 4. Nebulized Bronchodilators (Salbutamol or Albuterol) vs. Oral Bronchodilators, Nebulized Ipratropium Bromide, or Saline Placebo or No Treatment (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Ho et al., 1991[62] **Setting** Australia, Inpatient **Followup** Acute **Study Design** RCT-C **Length of enrollment** NR **Masking** Double-blind	To determine the effect of inhaled salbutamol on SaO_2 among infants with bronchiolitis	**Inclusion criteria** • Children admitted with cough and wheeze due to acute bronchiolitis within 5 days of admission • Clinical findings of hyperinflation with wheeze and crackles on auscultation • Respiratory syncytial virus isolated by immunoflorescence of a postnasal aspirate **Exclusion criteria** • Severely ill children and those with associated chronic disabilities • Prior history of respiratory problems	**Number** 21 completed study **Sex** NR **Mean age at enrollment (range)** 3 mos (3 wks to 6 mo) **Mean gestational age** NR **Comorbidities** None

Evidence Table 4. Nebulized Bronchodilators (Salbutamol or Albuterol) vs. Oral Bronchodilators, Nebulized Ipratropium Bromide, or Saline Placebo or No Treatment (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 13)** Nebulized salbutamol 2.5 mg/2 mL Nebulized placebo 2 mL normal saline All nebulizations with compressed air at flow rate of 6 L/min for 10 mins, followed by other treatment 30 mins later **Group B (n = 8)** Identical interventions in reverse order **Other treatment** Supplemental oxygen for 3 subjects	**Outcomes** **Primary outcome** • O_2 saturation at 5, 10, 15, 20, and 25 mins of first neb., during 10 mins. to next neb., 5, 10, 15, 20, and 25 mins of second nebulizstion – 11 of 13 given salbutamol first had a desaturation from baseline. – 8 of 8 given salbutamol second had desaturation from baseline **Subgroup analysis** None **Adverse events** NR, see primary outcome	**Significant differences between study groups** • No significant difference between groups for median maximum falls in SaO_2	**Quality** Fair **Significant differences at baseline** NR **Other comments** None

Evidence Table 4. Nebulized Bronchodilators (Salbutamol or Albuterol) vs. Oral Bronchodilators, Nebulized Ipratropium Bromide, or Saline Placebo or No Treatment (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Klassen et al., 1991[21] **Setting** Canada, Emergency department **Followup** Acute **Study design** RCT-P **Masking** Double-blind **Length of enrollment** Nov 1988 - Apr 1990	To test the hypothesis that nebulized salbutamol would provide greater short term improvement in respiratory status than a placebo in young children with bronchiolitis	**Inclusion criteria** • <24 months old • Wheezing present on auscultation at initial presentation and at least 5 mins later on examination by one of the investigators • RDAI > 3 **Exclusion criteria** • History of bronchodilator therapy • History of chronic disease (including asthma) • Severe respiratory disease as evidenced by a pulse rate > 200 beats/min, a respiratory rate > 80 breaths/min an RDAI score > 15, or profound lethargy	**Number** 85 eligible, 83 completed study **Sex** Salbutamol: 52% male (22/42) Placebo: 61% male (25/41) **Mean age at enrollment (mo ± SE)** Salbutamol: 7.3 ± 4.2 Placebo: 7.0 ± 3.9 **Mean gestational age (wk ± SE)** NR **Comorbidities** None

Evidence Table 4. Nebulized Bronchodilators (Salbutamol or Albuterol) vs. Oral Bronchodilators, Nebulized Ipratropium Bromide, or Saline Placebo or No Treatment (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 42)** Nebulized salbutamol 0.1 mg/kg added to 2 ml of 0.9% saline solution administered through updraft nebulizer for 5 to 8 mins with continuous flow of oxygen for 5 to 6 L/min Treatment repeated 30 mins after study entry **Group B (n = 41)** Nebulized saline 0.02 ml/kg of 0.9% saline, administered as above **Other treatment** If after 60 mins, improvement in RDAI score < 3, 0.1 mg/kg salbutamol with 2 ml of 0.9% saline	**Outcomes** **Primary outcome** • RDAI score at baseline, 30 mins and 60 mins (salbutamol vs. placebo) **Secondary outcomes** • Heart rate at baseline, 30 mins and 60 mins (salbutamol vs. placebo) • Respiratory rate at baseline, 30 mins and 60 mins (salbutamol vs. placebo) • Oxygen saturation at baseline, 30 mins and 60 mins (salbutamol vs. placebo) **Subgroup analysis** • Age < 1 yr – RDAI score significantly different at 30 mins, but not at 60 mins • Positive RSV status – RDAI score significantly different at 30 mins in RSV+ infants, but not at 60 mins **Adverse events** • Heart rate among salbutamol group significantly higher than placebo group (159 ± 16 vs. 151 ± 16)	**Significant differences between study groups** • Yes (P = 0.04 at 30 mins alone) • No • No • No • P = 0.01 at 30 mins, P = 0.08 at 60 mins • P = 0.04 at 30 mins, P = 0.1 at 60 mins • Yes (P = 0.03)	**Quality** Excellent **Significant differences at baseline** None **Other comments** None

Evidence Table 4. Nebulized Bronchodilators (Salbutamol or Albuterol) vs. Oral Bronchodilators, Nebulized Ipratropium Bromide, or Saline Placebo or No Treatment (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Schuh et al., 1990[44] **Setting** Canada, emergency department **Followup** Acute **Study design** RCT-P **Masking** Double-blind **Length of enrollment** Dec 1988 to Apr 1989	To evaluate the clinical response to nebulized albuterol in infants and young children with acute bronchiolitis	**Inclusion criteria** • 6 wks to 24 mon • History and clinical findings compatible with bronchiolitis **Exclusion criteria** • History of prematurity or mechanical ventilation • History of LRTI, wheezing or bronchodilatory therapy • History suggestive of chronic aspiration or cardiac disease • Current episode that started more than 2 wks prior to ED evaluation • Presentation between 12 midnight and 8 am	**Number** 40 randomized **Sex** Overall: 85% male (34/40) **Mean age at enrollment (mo ±SE)** Albuterol: 6.1 ± 1.3 Placebo: 5.3 ± 1.2 **Mean gestational age** NR **Comorbidities** None

Evidence Table 4. Nebulized Bronchodilators (Salbutamol or Albuterol) vs. Oral Bronchodilators, Nebulized Ipratropium Bromide, or Saline Placebo or No Treatment (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 21)** Nebulized albuterol 0.15 mg/kg/dose in 3 mL of 0.9% normal saline x 3 doses at 1 hr intervals **Group B (n = 19)** Nebulized saline 2 doses of saline 1 hr apart, followed by third dose of nebulized albuterol, as above All doses delivered by face mask and nebulizer, driven by oxygen at flow rate of 6 to 7 L/min over 15 mins **Other treatment** As indicated	**Outcomes** **Primary outcome** • Hospitalization (albuterol vs. placebo): – 19% (4/21) vs. 10.5% (2/19) • Mean percentage decrease in respiratory rate ± SD (albuterol vs. placebo) - After dose 1: 16.2 ± 3.3 vs. 15.5 ± 3.5 - After dose 2: 19.6 ± 3.4 vs. 8.0 ± 3.0 **Secondary outcomes** • Mean decrease in AMS ± SD (albuterol vs. placebo) - After dose 1: 0.7 ± 0.1 vs. 0.3 ± 0.1 - After dose 2: 0.86 ± 0.1 vs. 0.37± 0.1 • Mean decrease in wheeze score ± SD (albuterol vs. placebo) - After dose 1: 0.43 ± 0.1 vs. 0.32 ± 0.1 - After dose 2: 0.67 ± 0.1 vs. 0.47± 0.2 • Mean change in oxygen saturation ± SD (albuterol vs. placebo) - After dose 1: +0.71 ± 0.3 vs. -0.47 ± 0.3 - After dose 2: +0.76 ± 0.04 vs. -0.79 ± 0.5 • Mean change in heart rate ± SD (albuterol vs. placebo) - After dose 1: +4.3 ± 3.2 vs. -1.5 ± 3.0 - After dose 2: +7.8 ± 2.7 vs. -6.8 ± 3.8	**Significant differences between study groups** • NR • Not significant after dose 1, significant after dose 2 ($P = 0.01$) • Yes ($P = 0.01$ after dose 1, $P < 0.01$ after dose 2) • No significant differences • Yes ($P = 0.01$ after dose 1, $P = 0.01$ after dose 2) • Not significant after dose 1, significant after dose 2 ($P = 0.003$)	**Quality** Good **Significant differences at baseline** None **Other comments** Study powered to detect difference of 1 SD in respiratory rate

Evidence Table 4. Nebulized Bronchodilators (Salbutamol or Albuterol) vs. Oral Bronchodilators, Nebulized Ipratropium Bromide, or Saline Placebo or No Treatment (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Schuh et al., 1990[44] (continued)			

Evidence Table 4. Nebulized Bronchodilators (Salbutamol or Albuterol) vs. Oral Bronchodilators, Nebulized Ipratropium Bromide, or Saline Placebo or No Treatment (continued)

Intervention	Outcome	Quality
	Subgroup analysis • History of eczema - 19.4% decrease in respiratory rate for 13 patients with a family history of eczema vs. 19.7% for 8 patients without family history of eczema - 0.92 drop in accessory muscle score for 13 patients with a family history of eczema vs. 0.75 for 8 patients without family history of eczema	• NR
	Adverse events Increase in heart rate in albuterol group from mean of 153.2 to 160.9 beats/min	• NR

Evidence Table 4. Nebulized Bronchodilators (Salbutamol or Albuterol) vs. Oral Bronchodilators, Nebulized Ipratropium Bromide or Saline Placebo or no Treatment (continued)

Study characteristics	Stated objective of study	Inclusion/Exclusion criteria	Demographic Characteristics and Comorbidities
Author Schweich et al., 1992[56] **Setting:** United States, ED **Followup:** Acute **Study design** RCT-P **Length of enrollment** November 1989-March 1990 **Masking** Double-blind	To evaluate the efficacy of nebulized albuterol in the treatment of wheezing infants	**Inclusion criteria** • < 2 yrs old • Wheezing **Exclusion criteria** • Current sympathomimetic medicine • Chronic cardiac or pulmonary disease • Other major chronic diseases • Impending respiratory failure	**Number** 25 patients enrolled and randomized **Sex** Placebo: 50% male (6/12) Albuterol: 46% male (7/13) **Mean age at enrollment in mo.** Placebo: 8.7 Albuterol: 6.0 **Mean gestational age** NR **Comorbidities** None

Evidence Table 4. Nebulized Bronchodilators (Salbutamol or Albuterol) vs. Oral Bronchodilators, Nebulized Ipratropium Bromide or Saline Placebo or no Treatment (continued)

Intervention	Outcome		Quality
Intervention **Group A (n=12)** Albuterol 0.15 mg/kg in 3 ml of normal saline **Group B (n=13)** Placebo 0.03 ml/kg normal saline in 3 ml of normal saline 2 blinded treatments 30 mins. apart administered with continuous flow oxygen at 6 L/min Code broken 30 mins. after 2nd treatment, placebo patients given albuterol **Other treatment** Supplemental oxygen as needed	**Outcomes** **Primary outcomes** • Mean change in retraction score after first treatment ± SD (albuterol vs. placebo) – -0.54 ± 1.05 vs. -0.58 ± 0.79 • Mean change in retraction score after second treatment ± SD (albuterol vs. placebo) – -1.25 ± 1.35 vs -0.41 ± 0.90 • Mean change in total score after first treatment ± SD (albuterol vs. placebo) – -1.54 ± 2.36 vs. -1.58 ± 2.46 • Mean change in total score after second treatment ± SD (albuterol vs. placebo) – -4.08 ± 2.91 vs -1.33 ± 2.38 **Secondary outcomes** • Mean change in wheeze score after first treatment ± SD (albuterol vs. placebo) – -1.00 ± 2.00 vs. -1.00 ± 2.04 • Mean change in wheeze score after second treatment ± SD (albuterol vs. placebo) – -2.83 ± 2.55 vs. -0.92 ± 1.62 • Mean change in respiratory rate after first treatment (albuterol vs. placebo) – -1.8 vs. 2.9 • Mean change in respiratory rate after second treatment (albuterol vs. placebo) – -1.4 vs. -0.5 • Mean change in retraction rate after first treatment (albuterol vs. placebo) – -3.5 vs. 0.7 • Mean change in retraction rate after second treatment (albuterol vs. placebo) – 2.4 vs. -0.4	**Significant differences between study groups** • No, *P* value NR • No, *P* value NR • No, *P* value NR • Yes (*P* = 0.019) • No, *P* value NR • Yes (*P* = 0.039) • No, *P* value NR • No, *P* value NR • Yes (*P* = 0.018) • No, *P* value NR	**Quality** Good **Significant differences at baseline** None **Other comments** None

Evidence Table 4. Nebulized Bronchodilators (Salbutamol or Albuterol) vs. Oral Bronchodilators, Nebulized Ipratropium Bromide or Saline Placebo or no Treatment (continued)

Study characteristics	Stated objective of study	Inclusion/Exclusion criteria	Demographic Characteristics and Comorbidities
Author Schweich et al., 1992 (continued)			

Evidence Table 4. Nebulized Bronchodilators (Salbutamol or Albuterol) vs. Oral Bronchodilators, Nebulized Ipratropium Bromide or Saline Placebo or no Treatment (continued)

Intervention	Outcome		Quality
	• Mean change in heart rate after first treatment (albuterol vs. placebo)	• No, *P* value NR	
	• -14 vs. -9	• No, *P* value NR	
	• Mean change in heart rate after second treatment (albuterol vs. placebo)		
	– -13 vs. -15		
	Subgroup analysis		
	RSV status	• *P* value NR (n too low for statistical testing)	
	Adverse events		
	Small decrease in oxygen saturation in albuterol group		

Evidence Table 5. Nebulized Salbutamol or Albuterol plus Nebulized Ipratropium Bromide vs. Bronchodilators or Ipratropium Bromide Alone and/or Saline Placebo

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Chowdhury et al., 1995[63] **Setting:** Saudi Arabia, inpatient **Followup:** • Acute • Short term **Study design** RCT-P **Length of enrollment** Oct 1992 to Jan 1993 **Masking** Double-blind until 36 hrs, investigator unblended thereafter	To compare the efficacy of salbutamol, ipratropium bromide, and a combination of both vs. saline placebo in treating children hospitalized for bronchiolitis	**Inclusion criteria** • Admission for bronchiolitis defined as history of cough and/or wheeze, tachypnea, intercostals retractions, and on auscultation, rhonchi and rales • < 2 yrs • Presence of wheezing – audible or auscultation **Exclusion criteria** • Previous history of wheezing or use of bronchodilators • Chronic pulmonary disease • Congenital heart disease • CXR evidence of consolidation • Patients judged by admitting resident to be not sufficiently sick or to require intensive monitoring or therapy	**Number** 102 eligible, 89 completed study **Sex** Salbutamol[2]: 70% male (14/20) Ipratropium bromide: 70% male (16/23) Salbutamol + Ipratropium bromide: 70% male (16/23) Placebo: 77% male (17/22) **Mean age at enrollment (mo.± SE)** Salbutamol: 3.9 ± 2.3 Ipratropium bromide: 4.2 ± 2.4 Salbutamol + Ipratropium bromide: 3.6 ± 1.8 Placebo: 3.7 ± 2.3 **Mean gestational age** NR **Comorbidities** None

[2] S: Salbutamol
I: Ipratropium bromide
S+ I: Salbutamol and Ipratropium bromide
P: Placebo

Evidence Table 5. Nebulized Salbutamol or Albuterol plus Nebulized Ipratropium Bromide vs. Bronchodilators or Ipratropium Bromide Alone and/or Saline Placebo (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 20)** Salbutamol 0.15 mg/kg nebulized q. 6 hrs x 36 hrs **Group B (n = 23)** Ipratropium bromide 12.5 µg/kg nebulized q. 6 hrs x 36 hrs **Group C (n = 24)** Salbutamol + Ipratropium bromide nebulized Same dosing and schedule as Groups A and B **Group D (n = 22)** Placebo 0.3 mg/kg All doses with 100% oxygen at 6 to 7 L/min with pediatric nebulizers **Other treatment** NR	**Outcomes** **Primary outcome** • Mean duration of hospitalization in days ± SD - S: 4.5 ± 1.3 - I: 4.4 ± 1.4 - S+I: 4.6 ± 1.4 - P: 4.3 ± 1.1 • Clinical score at 30 mins, 60 mins, 6 hrs, 12 hrs, 24 hrs, 36 hrs **Subgroup analysis** • Age - < 3 mo. - > 3 mo. • RSV status **Adverse events** NR	**Significant differences between study groups** • No (P = 0.79) • No (P values ranged from 0.23 at 30 mins to 0.93 at 60 mins • No • No	**Quality** Fair **Significant differences at baseline** None **Other comments** Investigators unblinded at 36 hrs

Evidence Table 5. Nebulized Salbutamol or Albuterol plus Nebulized Ipratropium Bromide vs. Bronchodilators or Ipratropium Bromide Alone and/or Saline Placebo (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Schuh et al., 1992[64] **Setting** Canada, emergency department **Followup** Acute **Study Design** RCT-P **Length of enrollment** Dec 1989 - March 1991 **Masking** Double-blind	To determine whether infants with bronchiolitis would show a greater clinical response to nebulized albuterol-ipratropium combination compared with albuterol alone	**Inclusion criteria** • 6 wks to 24 months of age • Acute bronchiolitis, including upper respiratory tract infection with wheezing and respiratory distress (defined as respiratory rate ≥ 40 minute and/or chest retractions) • Presentation in ER between 8 am and midnight • First episode of wheezing **Exclusion criteria** • Very severe bronchiolitis, defined as either cyanosis at initial examination or initial respiratory rate ≥ 90 per minute with severe restrictions • History of mechanical ventilation after birth • Past history of wheezing or bronchodilator therapy • Concurrent cardiopulmonary disease • Recurrent aspiration • Respiratory distress started more than 2 wks prior to hospital visit	**Number** 72 enrolled, 69 completed study **Sex** NR **Mean age at enrollment (mos ± SD)** I+A[3]: 9.4 ± 6.1 P+A: 8.7 ± 5.2 **Mean gestational age** NR **Comorbidities** None

[3] I+A: Ipratropium bromide plus Albuterol
P+ A: Placebo plus Albuterol

Evidence Table 5. Nebulized Salbutamol or Albuterol plus Nebulized Ipratropium Bromide vs. Bronchodilators or Ipratropium Bromide Alone and/or Saline Placebo (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 36)** Nebulized albuterol 0.15 mg/kg and Nebulized ipatropium bromide 250 µg/kg; 2 doses 1 hr apart **Group B (n = 33)** Nebulized albuterol 0.15 mg/kg and saline placebo; 2 doses 1 hr apart All doses delivered via nebulizer with a tight - fitting small face mask, driven by oxygen at flow rate of 6-7 L/min **Other treatment** None reported	**Outcomes** **Primary Outcomes** • Mean change in respiratory rate from baseline to 120 mins ± SD (I+A vs. P+A) - 10.6 ± 10.0 vs. 8.6 ± 10.2 **Secondary Outcomes** Mean change from baseline to 120 mins in • Accessory muscle score • Wheeze score • SaO_2 increase • Heart rate increase • Overall responsiveness **Subgroup analysis** • Atopic history • Age - < 9 mo. vs. = 9 mo. **Adverse events** • Decline in oxygen saturation of 3% or more in both groups (2/36 vs. 3/33)	**Significant differences between study groups** • No ($P > 0.42$) • No • No • No • No • No • No • NR	**Quality** Good **Significant differences at baseline** None **Other comments** None

Evidence Table 5. Nebulized Salbutamol or Albuterol plus Nebulized Ipratropium Bromide vs. Bronchodilators or Ipratropium Bromide Alone and/or Saline Placebo (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Wang et al., 1992[65] **Setting** Canada, inpatient **Followup:** • Acute • Short term **Study design** RCT-P **Length of enrollment** NR **Masking** Double-blind	To examine the efficacy of inhaled bronchodilators in hospitalized patients using pulse oximetry and clinical score	**Inclusion criteria** • 2 mos - 2 yrs of age • First hospitalization for bronchiolitis • Did not have adequate improvement with emergency department management which always included salbutamol • Bronchiolitis diagnosed in the presence of expiratory wheezing of acute onset accompanied by signs of viral illness such as coryza **Exclusion criteria** • Known underlying cardiac or pulmonary disease • Transferred from another hospital • Condition rapidly deteriorating • Parental refusal or attending physician refusal	**Number** 150 eligible, 62 randomized **Sex** S + I:[4] 53% male (9/17) S: 57% male (8/14) I: 73% male (11/15) P: 38% male (6/16) **Mean age at enrollment** NR **Mean gestational age** NR **Comorbidities** None

[4] S+ I : Salbutamol and Ipratropium bromide
S: Salbutamol
I: Ipratropium bromide
P: Placebo

Evidence Table 5. Nebulized Salbutamol or Albuterol plus Nebulized Ipratropium Bromide vs. Bronchodilators or Ipratropium Bromide Alone and/or Saline Placebo (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 17)** Salbutamol + Ipratropium Salbutamol: 0.15 mg/kg in 2ml saline Ipratropium bromide: 125 µg if < 6mo., 250 µg if > 6mo. **Group B (n = 14)** Salbutamol 0.15 mg/kg in 2ml saline, then 0.5 ml or 1 ml saline I hr later **Group C (n = 15)** Ipratropium 0.03 ml/kg of saline in 2ml saline followed by ipratropium bromide 125 µg if < 6mo., 250 µg if > 6mo. **Group D (n = 16)** Placebo Saline, same volumes as indicated above All treatments administered through face mask and nebulizer driven by oxygen at flow rate of 6 - 7 L/min every 4 hrs of hospitalization or 3 days whichever came first **Other treatment** Routine care as needed, Ribavirin(1 patient), systematic steroids and theophylline(1 patient)	**Outcomes** **Primary outcome** • Mean duration of hospitalization in days ± SE - S+I: 2.5 ± 0.3 - S: 3.2 ± 0.4 - I: 2.4 ± 0.3 - P: 2.9 ± 0.4 **Secondary outcomes** • Mean change in clinical score • Mean change in oxygen saturation **Subgroup analysis** None **Adverse events** 1 child in salbutamol group had tremulousness, leading to withdrawal from study	**Significant differences between study groups** • No (*P* values NR) • No • Significantly greater for S+I vs. S (*P* = 0.002) and S+I vs. I (*P* = 0.04), but not S+I vs. P (*P* > 0.1). Significantly worse for S vs. P (*P* = 0.03)	**Quality** Good **Significant differences at baseline** Fewer boys in placebo group than other groups **Other comments** None

Evidence Table 6. Oral Corticosteroids vs. Placebo, With or Without Bronchodilators

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author: Berger 1998[70] **Setting** Israel, Emergency department at baseline **Followup** • Acute • Short term - 1 wk followup • Long-term - 2 yr telephone followup **Study design** RCT-P **Length of enrollment** Winter months 1993 - 1994 **Masking** Double-blind	To assess the Short term and Long-term effects of prednisone in infants suffering from mild to moderate bronchiolitis	**Inclusion criteria:** • 1 - 18 months of age (Bronchiolitis defined as first episode of wheezing associated with low - grade fever, rhinitis, tachypnea, and increased respiratory effort in a previously healthy infant during the winter months) **Exclusion criteria:** • Chronic cardiopulmonary disease, including asthma • Proven or suspected acute bacterial infection • Previous treatment with corticosteroids by any route • The presence of symptoms more than 7 days • Fever >38.5 C • Respiratory distress or total clinical score >7 • Infant requiring immediate medical care including oxygen	**Number** 42 enrolled, 38 completed 1 - wk followup, 28 contacted for 2 yr followup **Sex** NR **Mean age at enrollment (mos ± SD)** Prednisone: 5.2 ± 0.7 Placebo: 4.8 ± 0.9 **Mean gestational age** NR **Comorbidities** None

Evidence Table 6. Oral Corticosteroids vs. Placebo, With or Without Bronchodilators (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 20)** Prednisone Dose: 1 mg/kg PO BID x 3 d **Group B (n = 53)** Placebo Dose: Identically appearing solution and schedule **Other treatment** Inhaled albuterol solution Dose: 0.15mg/kg/dose q. 4 - 6 hrs via aerosol micromist nebulizer as indicated	**Outcomes** **Primary Outcomes** • Mean total score ± SD (prednisone vs. placebo) - Before treatment: 4.4 ± 2 vs. 1.95 ± 1.9 - After treatment: 1.95 ± 1.9 vs. 2.05 ± 3 - Mean change: 2.45 ± 0.12 vs. 2.45 ± 0.3 **Secondary Outcomes** • Accessory muscle score • Wheezing score • Respiratory rate • SaO_2 • Hospitalization rate – 25% vs. 11% • Parent's report of clinical status at 1 wk followup • Need for repeat evaluation in ER or outpatient clinic by 1 wk followup • Need for continued therapy at 1 wk followup • Recurrent respiratory symptoms at 2 yr followup – 35.7% vs. 28.6% **Adverse events** NR	**Significant differences between study groups** • No - *P* = 0.82 - *P* = 0.59 • No • No • No • No • NR • No • No • No • NR	**Quality** Good **Significant differences at baseline** None **Comments** Intent-to-treat analysis not used

Evidence Table 6. Oral Corticosteroids vs. Placebo, With or Without Bronchodilators (continued)

Study characteristics	Stated objective of study	Inclusion/Exclusion Criteria	Demographic Characteristics and Comorbidities
Author Daugbjerg et al., 1993[72] **Setting:** Denmark, inpatient **Followup:** Acute Short term **Study design** RCT-P **Length of enrollment** Winter seasons 1989-1990, 1990-1991 **Masking** Double-blind	To evaluate the effect of nebulized corticosteroids in combination with bronchodilators in the treatment of acute wheezing in children up to 18 months of age	**Inclusion criteria** • = 18 months • 5-15 kg • Symptom score of 3 or more • First or recurrent attack of wheezing **Exclusion criteria** • Pretreatment with steroids • Chronic lung disease or heart disease • Requiring assisted ventilation • Allergy to the test medication	**Number** 124 enrolled, 114 remaining for evaluation **Sex** P + T[5]: 71% male (22/31) B + T: 69% male (20/29) T: 70% male (19/27) P: 59% male (16/27) **Mean age at enrollment in mo. ± SD** P + T: 10.2 ± 4.5 B + T: 9.1 ± 4.4 T: 8.6 ± 3.6 P: 9.3 ± 3.9 **Mean gestational age** NR **Comorbidities** None

[5] P + T: Prednisolone + terbutaline
B + T: Budesonide + terbutaline
T: Terbutaline
P: Placebo

Evidence Table 6. Oral Corticosteroids vs. Placebo, With or Without Bronchodilators (continued)

Intervention	Outcome		Quality
Intervention **Group A (n=31)** Soluble prednisolone + placebo inhalation + terbutaline inhalation **Group B (n=29)** Soluble placebo + budesonide inhalation + terbutaline inhalation **Group C (n=27)** Soluble placebo + placebo inhalation + terbutaline inhalation **Group D (n=27)** Soluble placebo + placebo inhalation + normal saline inhalation Prednisolone: Day 1: 4-6 mg/kg Days 2,3: 1.6-2.6 mg/kg Budesonide: 0.5 mg q. 4 hrs until discharge or for five days Terbutaline: 0.12-0.2 mg/kg q. 4 hrs until discharge or for five days Both budesonide and terbutaline dissolved in normal saline, administered with oxygen at flow of 8 L/min via facemask. Night inhalation omitted if child was asleep, **Other treatment** NR	**Outcomes** **Primary outcomes** • Treatment failures (withdrawal from study because of deterioration of condition) – P + T: 16% (5/31) – B + T: 3% (1/29) – T: 11% (3/27) – P: 2% (14/27) • Mean days of hospitalization ± SD – P + T: 3.5± 1.4 – B + T: 3.5 ± 1.1 – T: 4.3 ± 1.4 – P: 4.1 ± 1.0 **Secondary outcomes** • Mean temperature ± SD – P + T: 37.4 ± 0.5 – B + T: 37.3 ± 0.6 – T: 37.5 ± 03 – P: 37.2 ± 0.5 • Mean respiratory rate ± SD – P + T: 39 ± 10 – B + T: 42 ± 8 – T: 41 ± 10 – P: 42 ± 5 • Mean respiratory rate ± SD – P + T: 39 ± 10 – B + T: 42 ± 8 – T: 41 ± 10 – P: 42 ± 5 **Subgroup analysis** • Age (Treatment failures for steroids groups vs. terbutaline + placebo) • Under 12 mos • Over 12 mos **Adverse events** None observed	**Significant differences between study groups** • Differences between all treatments vs. placebo are significant ($P < 0.01$), differences among treatment group not significant ($P = 0.1$) • Yes ($P = 0.04$) • Yes ($P = 0.02$) • Yes ($P = 0.08$) • Yes ($P = 0.009$)	**Quality** Good **Significant differences at baseline** None **Other comments**

Evidence Table 6. Oral Corticosteroids vs. Placebo, With or Without Bronchodilators (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Goebel et al., 2000[66] **Setting** United States, Emergency department **Followup** • Acute • Short term **Study design** RCT-P and open label albuterol **Length of enrollment** NR **Masking** Double-blind	To compare albuterol plus prednisolone versus albuterol plus placebo in young children with mild to moderate bronchiolitis	**Inclusion criteria** • = 23 mos of age • Symptoms of viral respiratory tract infection (rhinorrhea, cough, rectal temp to 38.5°C) during fall and winter months • First time wheezing not completely cleared by 1 dose of albuterol **Exclusion criteria** • History of - immune defect - neurologic disease with possible aspiration - gastroesophageal reflux - congenital or acquired heart or lung disease - mechanical ventilation - birth before 36 wks gestation • Fever > 38.5°C rectally, antibiotic therapy within 1 wk or antipyretics within 8 hrs • Evidence of bacterial infection • Emesis precluding administration of oral meds • Initial bronchiolitis score < 2 or > 9	**Number** 51 randomized, 48 at conclusion of study, 32 with complete data **Sex** Prednisolone plus albuterol: 75% male (18/24) Placebo plus albuterol: 67% male (16/24) **Median age at enrollment in months (range)** Prednisolone plus albuterol: 4.0 (0 - 13) Placebo plus albuterol: 4.5 (0 - 16) **Mean gestational age** NR **Comorbidities** None

Evidence Table 6. Oral Corticosteroids vs. Placebo, With or Without Bronchodilators (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 24)** Prednisolone plus albuterol Prednisolone: PO 2mg/kg/d PO divided BID x 5 days Albuterol: PO 0.3 mg/kg/day PO, divided TID or 0.15 mg/kg/dose QID by nebulizer **Group B (n = 24)** Placebo plus albuterol Placebo: Identically appearing solution, given at same dose and schedule Albuterol: Same as Group A **Other treatment** NR	**Outcomes** **Primary outcome** • Clinical scores (Prednisolone plus albuterol vs. placebo plus albuterol) - Day 0: 4.5 ± 1.7 vs. 4.9 ± 1.4 - Day 2: 2.7 ± 1.4 vs. 4.0 ± 1.5 • Clinical scores on Day 3 (values NR) • Clinical scores on Day 6 (values NR) **Subgroup analysis** • RSV status, culture positive vs. culture negative **Adverse events** • 1 subject in Grp A jittery, resolved after reduction of albuterol dose	**Significant differences between study groups** • Significant change for prednisolone plus albuterol between days 0 and 2 ($P < 0.05$), no significant change for placebo plus albuterol between days 0 and 2 ($P > 0.05$) • No (P value NR) • No (P value NR) • Trend toward improvement in Grp A regardless of RSV status but not statistically significant (P value NR)	**Quality** Good **Significant differences at baseline** None **Other comments** • Possible confounding effects from different methods of dosing albuterol • Incomplete followup • Post-hoc exclusion of 3 subjects

Evidence Table 6. Oral Corticosteroids vs. Placebo, With or Without Bronchodilators (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Klassen et al., 1997[69] **Setting** Canada, Inpatient **Followup** • Acute • Short term - 1 wk after discharge **Study design** RCT-P **Length of enrollment** Nov 1993 - Apr 1995 **Masking** Double-blind	To determine the clinical benefit of oral dexamethasone in children admitted to the hospital with bronchiolitis treated with nebulized salbutamol	**Inclusion criteria** • First episode of wheezing (lasting < 7days) • Clinical evidence of viral infection: - rhinorrhea - temp > 37.5°C • > 6 wks. to < 15 mo of age • O_2 < 95% at admission • RDAI > 6 **Exclusion criteria** • Underlying disease which affects cardiopulmonary status: - cystic fibrosis - bronchopulmonary dysplasia - congenital heart disease - immunodeficiency • Physician diagnosed asthma • Wheezing or cough treated by bronchodilators • Steroid treatment within 2 wks of admission	**Number** 72 eligible, 72 randomized, 67 completed study **Sex** Placebo: 47% male (15/32) Dexamethasone: 63% (22/35) **Mean age at enrollment in years** Placebo: 0.39 Dexamethasone: 0.39 **Mean gestational age** NR **Comorbidities** None

Evidence Table 6. Oral Corticosteroids vs. Placebo, With or Without Bronchodilators (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 32)** Placebo 70% sucrose solution **Group B (n = 53)** Dexamethasone 70% sucrose solution and dexamethasone, 0.5 mg/kg initial, 0.3 mg/kg q. morning until discharge **Other treatment** • Nebulized salbutamol (0.15mg/kg) q 4 hrs x first 24 hrs • 35% O_2 via plastic tent	**Outcomes** **Primary outcome** • Change in RDAI from baseline to 12, 24, 36, 48 and 60 hrs (placebo vs. dexamethasone) **Secondary outcomes** • Mean duration of hospitalization in hrs (range) (placebo vs. dexamethasone) - 48 (42, 54) vs. 57 (38, 76) • Readmission (placebo vs. dexamethasone) - 1 (3%) vs. 4 (11%) • Change in oxygen saturation from baseline to 12, 24, 36, 48 and 60 hrs (placebo vs. dexamethasone) • Change in respiratory rate at same intervals (placebo vs. dexamethasone) • Visits to MD/other health professionals (placebo vs. dexamethasone) - 24 (75%) vs. 29 (83%) • Salbutamol at discharge (placebo vs. dexamethasone) - 6 (19%) vs. 6 (17%) • Orciprenaline at discharge (placebo vs. dexamethasone) - 2 (6%) vs. 7 (20%) • Antibiotic use (placebo vs. dexamethasone) - 13 (41%) vs. 10 (29%) • IV hydration (placebo vs. dexamethasone) - 5 (16%) vs. 3 (8%) • Number of salbutamol inhalations after first 24 hrs - Details NR **Subgroup analysis** None **Adverse events** NR	**Significant differences between study groups** • No (*P* values range from 0.23 to 0.74) • No (*P* = 0.19) • No (*P* = 0.36) • No (*P* values range from 0.28 to 0.47) • No (*P* values range from 0.09 to 0.78) • No (*P* = 0.77) • No (*P* = 0.82) • No (*P* = 0.16) • No (*P* = 0.3) • No (*P* = 0.46) • No	**Quality** Excellent **Significant differences at baseline** None **Other comments** None

Evidence Table 6. Oral Corticosteroids vs. Placebo, With or Without Bronchodilators (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Schuh et al., 2002[23] **Setting** Canada, emergency department **Followup** • Acute • Short term – Day 7 at patient's home – Day 28 by telephone **Study design** RCT-P **Masking** Double-blind **Length of enrollment** Nov 1997 to Apr 2000	To investigate in outpatients younger than 2 yrs with acute bronchiolitis the clinical benefits of oral dexamethasone within 4 hrs of administration in the emergency department and after 5 d of continued therapy after discharge	**Inclusion criteria** • 8 wks - 23 mo • First wheezing episode associated with respiratory distress • RDAI rating of ≥ 6 at baseline • Presentation between 8 am to 9 pm **Exclusion criteria** • Previous history of wheezing or bronchodilator therapy • Prematurity • Neonatal ventilation • Chronic lung/cardiac disease • Aspiration • Neurologic/neuromus - cular problems • Immunodeficiency • Critically ill infants requiring immediate airway stabilization • Previous use of oral or inhaled corticosteroids • Exposure to varicella within 21 days before arrival	**Number** 71 eligible, 70 randomized, 67 evaluated at Day 7, 65 contacted on Day 28 **Sex** Dexamethasone: 56% male (20/36) Placebo: 68% male (23/34) **Mean age at enrollment (mo ± SE)** Dexamethasone: 6.1 ± 3.5 Placebo: 6.9 ± 3.9 **Mean gestational age (wk ± SE)** NR **Comorbidities** None

Evidence Table 6. Oral Corticosteroids vs. Placebo, With or Without Bronchodilators (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 36)** Oral dexamethasone 1 mg/kg in wild cherry syrup **Group B (n = 34)** Placebo syrup Identical color, texture, taste and smell **Other treatment** • Nebulized albuterol for all patients via vented nebulizer 2.5 mg per dose in 3 mL of normal saline with oxygen flow of 6 - 7 L/min with a tight - fitting face mask at 0, 30, 60 and 120 mins • Acetaminophen for fever as indicated • Discharged infants received dexamethasone in 0.6mg/kg/dose PO qd x 5 days or placebo as randomized, and albuterol 1.5 mg (0.3 µL) QID with same nebulizer	**Outcomes** **Primary outcome** • Rate of hospitalization (dexamethasone vs. placebo) – 44% (15/34) vs. 19% (7/36) **Secondary Outcomes** • Mean RACS from baseline to 240 mins ± SD (dexamethasone vs. placebo) – - 5.0 ± 3.1 vs. - 3.2 ± 3.7 • Mean RDAI from baseline to 240 mins ± SD (dexamethasone vs. placebo) – 5.4 ± 2.1 vs. 7.2 ± 2.8 • Mean RACS from baseline to Day 7 ± SD (dexamethasone vs. placebo) – - 8.9 ± 5.2 vs. - 9.3 ± 4.9 • Mean RDAI from baseline to Day 7 ± SD (dexamethasone vs. placebo) – 2.4 ± 3.1 vs. 2.6 ± 3.0 • Use of additional corticosteroids after discharge (dexamethasone vs. placebo) – 0/35 vs. 7/32 **Subgroup analysis** None **Adverse events** NR	**Significant differences between study groups** • Yes (P = 0.039) • Yes (P = 0.029) • No (P = 0.064) • No (P = 0.75) • No (P = 0.754) • Yes (P = 0.004)	**Quality** Excellent **Significant differences at baseline** Dexamethasone group more likely to have family history of atopy (P = 0.013) **Other comments** None

Evidence Table 6. Oral Corticosteroids vs. Placebo, With or Without Bronchodilators (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Van Woensel et al., 2000[67] **Setting** Telephone followup of original Inpatient sample **Followup** 5 yrs after original study (Aug 1998 to April 1999) **Study design** RCT-P **Length of enrollment of original study** Dec 1992 - April 1995 **Masking** Double-blind	A followup study of van Woensel[68] to investigate the effect of oral prednisolone vs. placebo during the acute phase of RSV bronchiolitis on the prevalence of wheezing during the first yr of life and asthma at age 5 yrs	**Inclusion criteria of original study** • < 2 yrs of age • Microbiologically proven RSV bronchiolitis • Bronchiolitis defined as first attack of acute tachypnea, wheezing and/or decreased breath sounds, cyanosis, and the use of accessory respiratory muscles in the presence of an apparent viral infection **Exclusion criteria of original study** • Use of corticosteroids (systemic or by inhalation) during the 2 mos before admission	**Number** 54 randomized in original study, 47 completed 5 yr followup **Sex** Prednisolone: 63% male (15/24) Placebo: 61% male (14/23) **Mean age at enrollment in yrs ± SE** Prednisolone: 4.9 ± 0.13 Placebo: 5.1± 0.16 **Mean gestational age** NR **Comorbidities** Prematurity, chronic lung disease, heart disease - Prednisolone: 5/24 (21%) - Placebo: 8/23 (35%)

Evidence Table 6. Oral Corticosteroids vs. Placebo, With or Without Bronchodilators (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 24 at followup)** Oral prednisolone 1 mg/kg/day in 2 divided doses x 7 days **Group B (n = 23 at followup)** Placebo Identical capsules, broken and dissolved in water **Other treatment** Supplemental oxygen, bronchodilators or antibiotics as indicated (NR in this study, details in original study)	**Outcomes** **Primary outcome** Wheezing outcomes in past 3 months (prednisolone vs. placebo) • No wheezing - 8/24 (33%) vs. 9/23 (39%) • Transient wheezing (wheezing during first[t] yr of life, stopped before age 5) - 2/24 (8%) vs. 4/23 (17%) • Persistent wheezing (wheezing during first yr of life, asthma or asthma attacks at age 5) - 10/24 (42%) vs. 7/23 (31%) • Late onset wheezing (no wheezing during first yr of life, asthma or asthma attacks at age 5) - 4/24 (17%) vs. 3/23 (13%) **Subgroup analysis** • Severe bronchiolitis - pretreatment severity score = 6 (range: 0 - 12) and those needing mechanical ventilation **Adverse events** None	**Significant differences between study groups** • No (*P* value NR) • No (*P* value NR) • No (*P* value NR) • No (*P* value NR) • No (*P* value NR)	**Quality** Fair **Significant differences at baseline** None **Other comments** None

Evidence Table 6. Oral Corticosteroids vs. Placebo, With or Without Bronchodilators (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author van Woensel et al., 1997[68] **Setting** Netherlands, Inpatient **Followup** Acute **Study design** RCT-P **Length of enrollment** Dec 1993 - April 1995 **Masking** Double-blind	To determine the effect of prednisolone on the clinical course of children admitted to hospital with RSV bronchiolitis, including patients with severe disease	**Inclusion criteria** • < 2 yrs of age • Microbiologically confirmed RSV bronchiolitis • Bronchiolitis defined as acute tachypnea, wheezing, and/or decreased breath sounds, cyanosis and use of accessory respiratory muscles, in the presence of an apparent viral infection **Exclusion criteria** • Corticosteroids (systemic or by inhalation) during the two mos before admission	**Number** 54 randomized, 53 included in efficacy analysis **Sex** Prednisolone: 67% male (18/27) Placebo: 41% male (11/27) **Median age at enrollment in mo. (inter - quartile range)** Prednisolone: 3.3 (1.4 - 5.9) Placebo: 3.9 (1.9 - 6.1) **Mean gestational age** NR **Comorbidities** Patients on ventilators at entry: 14, 7 in each group Bronchopulmonary dysplasia: 6/27 for prednisolone vs. 9/27 for placebo

Evidence Table 6. Oral Corticosteroids vs. Placebo, With or Without Bronchodilators (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 27)** Oral prednisolone 1mg/kg/day in two divided doses x 7 days **Group B (n = 27)** Placebo Identical capsules, broken and dissolved in water **Other treatment** Supplemental oxygen, bronchodilators or antibiotics as indicated	**Outcomes** **Primary outcome** • Mean decline in symptom score among non-ventilated patients ± SE (prednisolone vs. placebo, N = 39) – - 1.2 ± 0.2 vs. 0.6 ± 0.2 • Mean duration of hospitalization in days among non-ventilated patients ± SE (prednisolone vs. placebo) – 7.3 ± 1.2 vs. 8.3 ± 0.9 • Mean duration of hospitalization in days among ventilated patients ± SE (prednisolone vs. placebo) – 11.0 ± 0.7 vs. 17.0 ± 2.0 • Mean duration of mechanical ventilation in days ± SE (prednisolone vs. placebo) – 4.7 ± 1.1 vs. 6.3 ± 1.6 **Secondary outcomes** • Duration of supplemental oxygen • Bronchodilator use • Antibiotic use **Subgroup analysis** • Baseline severity score • Family history of atopic disease • IgE level at entry **Adverse events** 1 death unrelated to intervention	**Significant differences between study groups** • Yes ($P = 0.02$) • No ($P < 0.54$) • Yes ($P < 0.01$) • No ($P < 0.556$) • No • No • No • No • No • No	**Quality** Good **Significant differences at baseline** NR **Other comments** Ill study group with high degree of comorbidity

Evidence Table 7. Parenteral Dexamethasone vs. Placebo

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author De Boeck et al., 1997[48] **Setting:** Belgium, Inpatient **Followup** Acute **Study design** RCT-P **Length of enrollment** Epidemic of 1991 to 1992 **Masking** Double-blind	To reevaluate the efficacy of intravenous corticosteroids in previously healthy infants without underlying disease hospitalized with proven RSV primary infection	**Inclusion criteria** • < 24 months admitted to hospital • Signs of bronchiolitis: prodromal rhinorrhea, cough, or low-grade fever followed by at least 2 of the following signs: chest retractions, tachypnea, wheezing, or rales • Detection of RSV in nasal wash taken on admission by ELISA • First episode of wheezing or shortness of breath • Onset of illness within previous 5 days **Exclusion criteria** • Underlying heart, lung, or immune disorder • Premature (< 34 wks gestational age)	**Number** 32 enrolled, 29 completed study **Sex** NR **Median age at enrollment in days (range)** Dexamethasone: 186 (111 - 224) Placebo: 213 (133 - 267) **Mean gestational age (wks ± SE)** NR **Comorbidities** None

Evidence Table 7. Parenteral Dexamethasone vs. Placebo (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 51)** Dexamethasone 0.6 mg/kg IV x 2 on Day 1, 0.015mg/kg on Days 2 and 3 **Group B (n = 53)** Placebo Details NR **Other treatment** • Salbutamol (0.5%), 0.25 ml and ipratropium bromide (0.025%), 0.5 ml aerosolized every 6 hrs • Oxygen to maintain oxygen saturation > 90% • Antibiotics as indicated • Standardized concomitant therapy	**Outcomes** **Primary outcome** • Mean duration of hospitalization in days ± SE (dexamethasone vs. placebo) - 6.0 ± 0.3 vs. 6.6 ± 0.7 **Secondary outcomes** • Improvement in clinical scores after aerosol • Respiratory rate • Oxygen saturation • Pulmonary function tests • Treatment with antibiotics **Subgroup analysis** None **Adverse events** NR	**Significant differences between study groups** • No (*P* value NR) • No • No • No • No	**Quality** Fair **Significant differences at baseline** None **Other comments** None

Evidence Table 7. Parenteral Dexamethasone vs. Placebo (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author: Roosevelt et al., 1996[43] **Setting** United States, Inpatient **Followup** • Acute • Short term - telephone followup 10 - 14 days after discharge **Study design** RCT-P **Length of enrollment** Dec 1993 to March 1994, Dec 1994 to March 1995 **Masking** Double-blind	To assess the efficacy and safety of dexamethasone in infants with bronchiolitis who require hospital management	**Inclusion criteria** • < 12 mos of age • first episode of wheezing **Exclusion criteria** • infants < 4 wks old • admitted to ICU • known history of congenital heart disease • history of intubation, ventilation, supplemental oxygen	**Number** 122 enrolled, 118 completed study **Sex** Dexamethasone: 63% male (41/65), Placebo: 62% male (33/53) **Mean age at enrollment (mo.± SD)** Dexamethasone: 5.3 ± 3.7 Placebo: 5.0 ± 2.5 **Mean gestational age** NR **Comorbidities** None

Evidence Table 7. Parenteral Dexamethasone vs. Placebo (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 65)** Dexamethasone Dose: 1 mg/kg IM q day x 3 days **Group B (n = 53)** Placebo Dose: Identically appearing solution and schedule **Other treatment** Antibiotics and nebulized bronchodilators used as needed	**Outcomes** **Primary outcome** • Time to resolution (number of 12 hr periods needed for SaO_2 >95% while receiving no supplemental oxygen, accessory muscle score of 0, wheeze of 0 or 1, and resumption of normal feeding) - Hazard ratio (95% C.I.): 1.3 (0.9 - 1.3) • Duration of oxygen therapy - Hazard ratio (95% C.I.): 0.9 (0.6 - 1.4) **Secondary outcomes** • Use of antibiotics, nebulized beta-agonist and other bronchodilators • Visits to health professionals for respiratory symptoms • Steroid use started in hospital after study completed • Symptoms reported by parents at 14 day followup **Subgroup analyses** • RSV status • Hypoxia (<95% SaO_2) • Family history of atopy • RSV and family history of atopy **Adverse events** Positive stool for occult blood in 2/65 for dexamethasone vs. 1/53 for placebo	**Significant differences between study groups** • No (P = 0.22) • No (P = 0.74) • No • No • No • No • No • No • No • No	**Quality** Good **Significant differences at baseline** Dexamethasone group had significantly more patients with SaO_2 <95% (79% vs. 59%, P = 0.02) **Other comments** None

Evidence Table 8. Nebulized Corticosteroids vs. Placebo or Usual Care

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Cade et al., 2000[71] **Setting** United Kingdom, Inpatient **Followup** United Kingdom **Study Design** RCT-P **Length of enrollment** NR **Masking** Double-blind	To evaluate the short and long term effects of giving a short course of nebulized budesonide to hospitalized infants with RSV positive bronchiolitis	**Inclusion criteria** • < 12 months of age • Confirmed RSV infection • Randomization within 12 hrs of admission **Exclusion criteria** • Previous hospital admissions with respiratory tract illness • Chronic respiratory illness • Congenital heart disease • Prematurity • Pre-existing immunodeficiencies • Recent exposure to varicella or tuberculosis • Prolonged exposure to systemic steroids	**Number** 165 enrolled, 161 completed study **Sex** 56% male (45/82) for budesonide 60% male (47/79) for placebo **Mean age (days ± SD)** Budesonide: 130 ± 85 Placebo: 120 ± 84 **Mean gestational age** NR **Comorbidities** NR

Evidence Table 8. Nebulized Corticosteroids vs. Placebo or Usual Care (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 82)** Budesonide 1mg nebulized twice daily until 14 days after discharge, up to a maximum of 21 days **Group B (n = 79)** Placebo Nebulized vehicle given in place of budesonide, using same schedule as Group A **Other interventions** Ipratropium bromide, beta agonists, antibiotics, oral or intravenous steroids as indicated	**Outcomes** **Primary outcomes** • Coughing and wheezing episodes in 12 mo followup period (budesonide vs. placebo) - 99% vs. 99% **Secondary outcomes** • Days from first nebulization until fit for hospital discharge - Hazard ratio (95% C.I.): 1.1 (0.80 - 1.51) • Time to become asymptomatic for 48 hrs - Hazard ratio (95% C.I.): 1.41 (0.98 - 2.04) • Mean number of coughing/ wheezing episodes from discharge to day 28 ± SD (budesonide vs. placebo) - 17.0 ± 7.6 vs. 17.1 ± 8.5 • Readmission for respiratory morbidity over 12 months (budesonide vs. placebo) - 16% vs. 17% • Mean visits for respiratory morbidity(budesonide vs. placebo) - 4 vs. 4.5 • Prescription for bronchodilator (budesonide vs. placebo) - 60% vs. 67% • Prescription for steroids(budesonide vs. placebo) - 50% vs. 60% **Subgroup analysis** • Outcomes (1) Respiratory related readmissions (2) GP respiratory visits by - Initial severity score - Duration of symptoms at presentation - Atopic history - Exposure to cigarette smoke or damp in household **Adverse events** NR	**Significant differences between study groups** • No (*P* =0.98) • No (*P* = 0.51) • No (*P* = 0.07) • No (*P* = 0.91) • No (*P* = 0.78) • No (*P* = 0.29) • No (*P* = 0.42) • No (*P* = 0.23) • No significant differences between budesonide and placebo for both outcomes by all subgroups	**Quality** Good **Significant differences at baseline** More furry pets in placebo households (36% vs. 21%) **Other comments** None

Evidence Table 8. Nebulized Corticosteroids vs. Placebo or Usual Care (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Fox et al., 1999[73] **Setting:** United Kingdom, inpatient at baseline, diary records and Outpatient followup **Followup** • Long term - 12 months **Study design** RCT-P **Length of enrollment** NR **Masking** Double blind	To assess the efficacy of inhaled budesonide in reducing the incidence of coughing and wheezing episodes during the first yr after acute viral bronchiolitis	**Inclusion criteria** • = 12 mo of age • Clinical diagnosis of acute viral bronchiolitis requiring hospital admission • Clinical diagnosis based on tachypnea (respiratory rate > 40/mins), chest hyperinflation, soft tissue recession, and bilateral crackles, with or without wheezes **Exclusion criteria** • Underlying cardiopulmonary disease • Congenital heart disease • Bronchopulmonary dysplasia • Cystic fibrosis • History of respiratory problems in the neonatal period • Requiring mechanical ventilation during present illness	**Number** 60 enrolled, 49 patients with full followup **Sex** Budesonide: 77% male (20/26) Placebo: 50% male (14/28) **Median age at enrollment in weeks (range)** Budesonide: 11 (1-38) Placebo: 10 (3-42) **Mean gestational age** NR **Comorbidities** None

Evidence Table 8. Nebulized Corticosteroids vs. Placebo or Usual Care (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 26)** Budesonide 200 µg 1 puff BID x 8 wks by metered dose inhaler and modified spacer and face mask system **Group B (n = 28)** Placebo Similar schedule and route as intervention **Other treatment** Routine supportive care as needed	**Outcomes** **Primary outcome** • Number with wheezing/cough at (budesonide vs. placebo) - 1 mo: 4/26 vs. 5/28 - 2 mo: 11/26 vs. 11/28 - 6 mo: 15/26 vs. 12/27 - 12 mo: 21/25 vs. 12/24 • Hospital admissions by 12 mo followup (budesonide vs. placebo): - 5/25 vs. 6/24 • Number with =3 symptom episodes at 12 mo followup (budesonide vs. placebo): - 11/25 vs. 6/24 • Median (range) symptom episodes at 12 mo followup (budesonide vs. placebo): - 2 (0-13) vs. 1(0-11) • Median (range) symptom days at 12 mo. followup (budesonide vs. placebo): - 18(0-106) vs. 9(0-90) **Subgroup analysis** • Logistic regression of symptoms at 12 mo. followup, controlling for differences in sex (no significant differences for sex at baseline, but 24/30 males vs. 9/19 females had symptoms at followup and more males got budesonide) **Adverse events** • Admission to hospital with viral gastroenteritis (1/24 in placebo group) • Mild coughing and wheezing (1/25 in budesonide group)	**Significant differences between study groups** • Significant only at 12 mo - (*P* = 1.0) - (*P* = 0.82) - (*P* = 0.49) - (*P* = 0.03) • No (*P* = 0.94) • No (*P* = 0.27) • Yes (*P* = 0.02) • No (*P* = 0.08) • No (*P* = 0.051)	**Quality** Fair **Significant differences at baseline** None **Other comments** • When possible confounding effect of sex is controlled, diff between study groups in symptoms at 12 mo reduces in significance • 11 patients concluded from final data analysis for loss to followup, partial loss to followup or poor compliance

Evidence Table 8. Nebulized Corticosteroids vs. Placebo or Usual Care (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Kajosaari et al., 2000[74] **Setting** Finland, needing hospital treatment at baseline, Outpatient at 2 and 6 mo, telephone interview at 2 yrs **Followup** • Acute • Long-term – 2 mo – 6 mo – 2 yrs **Study design** RCT - nonplacebo **Length of enrollment** NR **Masking** None	To determine whether inhaled corticosteroids in infants during and after the acute phase of RSV infections influences their subsequent respiratory status	**Inclusion criteria** • 0 - 9 months of age • Needing hospital treatment because of RSV bronchiolitis • Healthy, full-term babies **Exclusion criteria** • Mechanical ventilation • Pre-term babies	**Number** 117 randomized and initial study size, 109 completed followup study at 2 yrs **Sex** NR **Mean age range at enrollment in months** Group A: 0.5 - 5.2 Group B: 0.3 - 6.4 Group C: 0.5 - 5.9 **Mean gestational age** NR **Comorbidities** None

Evidence Table 8. Nebulized Corticosteroids vs. Placebo or Usual Care (continued)

Intervention	Outcome		Quality
Intervention	**Outcomes**	**Significant differences between study groups**	**Quality**
Group A (n = 41 at baseline, 38 at 2 yr followup)			Poor
Symptomatic treatment: oxygen, bronchodilators and/or racemic epinephrine	**Primary outcome**		**Significant differences at baseline**
	• Asthma inhalation therapy at 2 yrs (Grp A vs. Grp B vs. Grp C)	• Yes	Grp A had lower proportion of atopic heredity
Group B (n = 40 at baseline, 39 at 2 yr followup)	- 37% (14/38) vs. 18% (7/39) vs. 12% (4/32)		
Symptomatic treatment + inhaled budesonide	- Odds ratio (95% C.I.) of Grp A vs. Grp C: 4.08 (1.39 - 11.98)	- Grp A vs. Grp B: *P* = 0.006	**Other comments**
	- Odds ratio (95% C.I.) of Grp A vs. Grp B: 2.67 (0.98 - 7.27)	- Grp A vs. Grp C: *P* = 0.01	8 children concluded from final analysis: 3 due to loss to followup, 1 for RSV infection, 1 for prematurity, 3 for non-compliance
500 µg TID x 7 days	- Odds ratio (95% C.I.) of Grp A vs. (Grp B + Grp C): 3.18 (1.25 - 8.12)	- NR	
Group C (n = 36 at baseline, 32 at 2 yr followup)	• Atopic status at 6 mo	• NR	
Symptomatic treatment + inhaled budesonide	- Grp 1: 13% (5/38)		
	- Grp 2: 28% (11/39)		
500 µg BID x 2 mos	- Grp 3: 25% (8/32)		
Other treatment	**Secondary outcomes**		
Routine care as indicated	NR		
	Subgroup analysis		
	None		
	Adverse events		
	NR		

Evidence Table 8. Nebulized Corticosteroids vs. Placebo or Usual Care (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Reijonen 1996[75] **Setting** Finland, inpatient **Followup** • Acute • Long-term - Outpatient followup at 6 and 16 wks **Study design** RCT non-placebo **Masking** Investigators not blinded, unclear for others	To determine whether early treatment with nebulized cromolyn sodium or budesonide reduces the frequency of wheezing episodes among infants with acute bronchiolitis	**Inclusion criteria** • Hospitalized patients age 1 - 23 mos • Clinical criteria of acute bronchiolitis: wheezing and respiratory distress in patient with acute URTI **Exclusion criteria** • Chronic cardiorespiratory disease (asthma, BPD, CHD) • Received medication for any pulmonary disease	**Number** 100 enrolled, 98 at 6 wk followup, 92 at 16 wk followup **Sex** Cromolyn sodium: 65% male (22/34) Budesonide: 65% male (22/34) Control: 81% male (26/32) **Mean age at enrollment (mo± SD)** Cromolyn sodium: 9.6 ± 6.2 Budesonide: 10.1 ± 5.0 Control: 11.1 ± 6.9 **Mean gestational age** NR **Comorbidities** • 13% with previous history of wheezing (no sig. diffs. among groups) • 29% with atopy (no sig. diffs. among groups)

Evidence Table 8. Nebulized Corticosteroids vs. Placebo or Usual Care (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 34)** Cromolyn sodium Dose: 20mg QID x 8 wks then 20mg TID x 8 wks **Group B (n = 34)** Budesonide Dose: 500µg BID x 8 wks then 250µg BID x 8 wks **Group C (n = 32)** No treatment All meds given with face mask using a foot pump and pumping rate at 60/minute **Other treatment** • Oral bronchodilating drugs advised for 1 wk after acute bronchiolitis, as needed thereafter • Oral slow - release theophylline as needed	**Outcomes** **Primary outcome** • Mean days with symptomatic wheezing (cromolyn sodium vs. budesonide vs. no treatment) at - 1 to 4 wks: 5.1 vs. 4.9 vs. 5.3 - 5 to 8 wks: 4.5 vs. 3.5 vs. 3.9 - 9 to 16 wks: 9.1 vs. 7.5 vs. 2.3 - 13 to 16 wks: 2.4 vs. 2.2 vs. 3.0 • At least one Physician-diagnosed wheezing episode at 1 - 8, 9 - 16 and 1 - 16 wks - Cromolyn sodium vs. control at 9 - 16 wks: 6/31 vs. 14/31 - Budesonide vs. control at 9 to 16 wks: 5/31 vs. 14/31 • Repeated (2 or more) Physician-diagnosed wheezing episodes at 1 to 16 wks - Cromolyn sodium vs. control: 6/31 vs. 12/31 - Budesonide vs. control 3/31 vs. 12/31 • Hospital care for repeat wheezers (detail NR) **Subgroup analysis** • Age (> 1 yr vs. < 1 yr) • Atopic patients (n = 36) - Physician-diagnosed wheezing: Cromolyn sodium: 4/13 Budesonide:2/11 Control: 8/12 - Hospitalized for treatment of wheezing: Cromolyn sodium: 1/13 Budesonide:1/11 Control: 7/12 **Adverse events** NR	**Significant differences between study groups** • No – $P = 0.97$ – – $P = 0.87$ – – $P = 0.55$ – $P = 0.87$ • Significantly diff. from control group only at 9 - 16 wks: Cromolyn sodium vs. control ($P = 0.01$), Budesonide vs. control ($P = 0.01$) • Significantly diff. only for budesonide vs. control group ($P = 0.01$) • No (P values NR) • No • Not significant for Physician-diagnosed wheezing, ($P > 0.05$), significant for hospitalization ($P < 0.05$)	**Quality** Fair **Significant differences at baseline** None **Other comments** • No placebo group • Investigators not blinded • Percentage of children with history of atopy high • All enrollees had participated in a Racemic epinephrine vs. Albuterol trial prior to enrollment in this study[54]

Evidence Table 8. Nebulized Corticosteroids vs. Placebo or Usual Care (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Richter et al., 1998[76] **Setting** United Kingdom, Inpatient at baseline, Outpatient at followup **Followup** • Acute • Short term - 6 wks • Long-term - 6 mo **Study design** RCT-P **Length of enrollment** NR **Masking** Double-blind	To determine the effectiveness of nebulized budesonide in reducing the severity and duration of lower respiratory symptoms in acute bronchiolitis and in preventing postbronchiolitic cough and wheezing	**Inclusion criteria** • < 12 months of age • No previous wheezing episodes • Hospitalized with clinical features of bronchiolitis, (tachypnea, recession, wheezing, and crepitations) **Exclusion criteria** • Congenital abnormality • Preexisting pulmonary disease • Immune deficiency • Need for assisted ventilation	**Number** 40 randomized, 40 completed study **Sex** Budesonide: 57% male (12/21) Placebo: 53% male (10/19) **Median age at enrollment in wks (range)** Budesonide: 16.3 (4.4 to 40.6) Placebo: 10.8 (3.6 to 29.1) **Median gestational age in wks (range)** Budesonide: 38 (34 to 41) Placebo: 39 (36 to 42) **Comorbidities** None

Evidence Table 8. Nebulized Corticosteroids vs. Placebo or Usual Care (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 21)** Nebulized budesonide 1 mg in 2 mL BID x 5 days, then 500 µg/mL BID for remainder of 6 wk period **Group B (n = 19)** Placebo 2 mL q. 12 hrs x 6 wks **Method of delivery** Side Stream nebulizer with face masks with oxygen flow of 6 L/mins, and Portaneb compressors after discharge **Other treatment** Other treatment as needed, including terbutaline	**Outcomes** **Primary outcome** *Acute* • Days in oxygen after trial entry (budesonide vs. placebo) - 1.0 (0 to 7) vs. 1.0 (0 to 6) • Maximum oxygen requirement after trial entry (budesonide vs. placebo) - 30% (21% to 60%) vs. 30% (21% to 50%) • Median (range) duration of hospitalization in days from trial entry to discharge (budesonide vs. placebo) - 2.0 (1 - 11) vs. 3.0 (1 - 7) • Change in clinical scores 48 hrs after trial entry (range) (budesonide vs. placebo) - - 2.0 (-6 - +6) vs. - 1.0 (-9 - +2) *Chronic - 6 wks* • Infants not given bronchodilators during 6 wk treatment (budesonide vs. placebo) - 9 (45%) vs. 8 (42%) • Infants not given bronchodilators on 5+ occasions during 6 wk treatment (budesonide vs. placebo) - 10 (50%) vs. 4 (21%) • Mean daily symptom scores (budesonide vs. placebo) - 2.7 vs. 1.5 • Median no. of symptom - free days (budesonide vs. placebo) - 8.5 vs. 12.0 *Chronic - 6 mos* • Prevalence of wheeze during 6 mo followup (budesonide vs. placebo) - 15 (75%) vs. 15 (79%) • Infants given bronchodilators during 6 mo followup (budesonide vs. placebo) - 13 (65%) vs. 10 (53%)	**Significant differences between study groups** • No (*P* = 0.29) • No (*P* = 0.33) • No (*P* = 0.65) • No (*P* = 0.92) • No (*P* = 1.0) • No (*P* = 0.1) • No (*P* = 0.94) • No (*P* = 0.57) • No (*P* = 1.0) • No (*P* = 0.52)	**Quality** Good **Significant differences at baseline** None **Other comments** None

Evidence Table 8. Nebulized Corticosteroids vs. Placebo or Usual Care (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Richter et al., 1998[76] (continued)			

Evidence Table 8. Nebulized Corticosteroids vs. Placebo or Usual Care (continued)

Intervention	Outcome	Quality
	• Infants given inhaled + oral steroids during 6 mo followup (budesonide vs. placebo) - 3 (15%) vs. 3 (16%)	• No (*P* = 1.0)
	• Infants readmitted for respiratory problems (budesonide vs. placebo) - 10 (50%) vs. 2 (10.5%)	• Yes (*P* = 0.01)
	• Median scores for cough and wheeze (budesonide vs. placebo) - 10.0 vs. 10.0	• No (*P* = 1.0)
	• Median scores for wheeze only (budesonide vs. placebo) - 4.5 vs. 5.0	• No (*P* = 0.97)
	Subgroup analysis • Family history of atopy - prevalence of wheeze - median score for cough and wheeze - median score for wheeze alone	• No significant differences for any outcome
	Adverse events • Median growth in cm/wk (budesonide vs. placebo) - 0.43 vs. 0.47	• No (*P* = 0.16)

Evidence Table 8. Nebulized Corticosteroids vs. Placebo or Usual Care (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Wong et al., 2000[77] **Setting** United Kingdom, inpatient **Followup** • Acute • Long term at 3, 6, 9, and 12 mo after entry **Study design** RCT-P **Masking** Double-blind **Length of enrollment** Mar 1994 - Apr 1996	To assess the efficacy and safety of inhaled fluticasone propionate during the trial period, and the following 9 mos	**Inclusion criteria** • Age 2 wks to 12 mo • First episode of lower respiratory tract infection **Exclusion criteria** • Birth before 36 wks of gestation • CHD or syndromic abnormalities • Established systemic or chronic illnesses • Treatment with corticosteroids before entering study • Mechanical ventilation before entering study • Parents unable to use inhaler/babyhaler	**Number** 48 randomized, 43 completed trial, 41 in long-term study **Sex** Fluticasone propionate: 54% (13/24) Placebo: 58% (14/24) **Mean age at enrollment in mo. (range)** Fluticasone propionate: 3.8 (0.9 - 4.7) Placebo: 3.9 (1.0 - 10.9) **Mean gestational age in wks. (range)** Fluticasone propionate: 39.4 (36.8 - 43.0) Placebo: 39.7 (36.0 - 42.0) **Comorbidities** None

Evidence Table 8. Nebulized Corticosteroids vs. Placebo or Usual Care (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 21)** Fluticasone propionate (FP) 3 puffs of 50 µg BID x 3 mo. from MDI administered via the babyhaler (spacer) with a face mask attachment **Group B (n = 23)** Placebo Type of placebo not reported, same delivery as above **Other treatment** Bronchodilators, steroids and/or antibiotics as indicated	**Outcomes** **Primary outcome** • Overnight oxygen saturation (details NR) • Night cough events (single cough) during treatment and followup at 3, 6, 12, 24 and 36 wks from baseline • Night cough episodes (period of coughing with = 10 seconds before and after) during treatment and followup at 3, 6, 12, 24 and 36 wks from baseline • Symptom frequency as recognized by parent (FP vs. Placebo) – Cough: 95.8 vs. 89.6 – Wheeze: 99.7 vs. 94.5 **Secondary outcomes** • Lung function tests 6 mo. after discharge • Use of rescue respiratory medications ($ß_2$ - agonists, corticosteroids, antibiotics) • Increase in respiratory symptoms leading caregivers to seek medical advice • Hospital admissions at 9 mos after treatment • Received treatment at 9 mos after treatment **Subgroup analysis** None **Adverse events** Oral candidiasis (2 FP patients)	**Significant differences between study groups** • No (*P* values NR) • No (*P* values range from 0.20 - 0.64) • Significant only at 36 wks (*P* = 0.05), not significant at other time periods • No (*P* values NR) • No • No, however more placebo subjects received bronchodilators /steroids, diff not significant (*P* = 0.07) • No • No • No	**Quality** Good **Significant differences at baseline** None **Other comments** • Missing data value extrapolated from previous visit • 3 FP patients withdrawn, 2 placebo patients withdrawn

Evidence Table 9. Ribavirin vs. Placebo

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Barry et al., 1986[46] **Setting** United Kingdom, multi-center inpatient **Followup** • Acute • Short term – length of hospitali-zation **Study design** RCT-P **Length of enrollment** NR **Masking** Double-blind	To test the efficacy of ribavirin in infants with acute bronchiolitis	**Inclusion criteria** • Diagnosis of bronchiolitis defined as history of URTI followed by cough, breathlessness and wheezing and clinical signs of chest overinflation, tachypnea, rhonchi or crepitations. **Exclusion criteria** • < 2 wks old • < 41 wks since mother's last menstrual period • Underlying chest or heart disease • Previous bronchiolitis • Immune defect • > 72 hrs of chest symptoms	**Number** 26 enrolled, 26 completed study **Sex** Ribavirin: 64% male (9/14) Placebo: 83% male (10/12) **Age at enrollment** NR **Mean gestational age** NR **Comorbidities** None

Evidence Table 9. Ribavirin vs. Placebo (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 14)** Aerosolized ribavirin 20 mg/ml **Group B (n = 12)** Saline placebo Both administered for 18 out of 24 hrs for at least 3 days **Other treatment** Oxygen and antibiotics as indicated	**Outcomes** **Primary outcome** • Median hrs to sustained improvement (ribavirin vs. Placebo) in – cough (24 vs. 66) – nasal discharge – feeding – nasal flare – wheeze – chest recession – rhonchi – crepitations (23 vs. 44) • Change in respiratory rate – Graphical data presented with text, specific values not detailed • Change in heart rate – Graphical data presented with text, specific values not detailed **Subgroup analysis** RSV status **Adverse events** Transient redness of eyelids possibly from deposition of the drug on the skin (1 ribavirin patient)	**Significant differences between study groups** • Not significant except for median hrs to sustained improvement in cough and crepitations ($P < 0.05$) • Yes ($P < 0.05$) • No • Significant difference only for decrease in chest recession ($P < 0.05$)	**Quality** Fair **Significant differences at baseline** None **Other comments** Details of randomization protocol not provided; however, assignment to treatment or control was specifically to minimize differences in age, arterialized capillary CO_2, respiratory rate, and interval since onset of chest symptoms

Evidence Table 9. Ribavirin vs. Placebo (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Everard et al., 2001[78] **Setting** United Kingdom, Inpatient at baseline, Outpatient at followup **Followup** • Acute • Short term 6 wks • Long-term 6 mos **Study design** RCT-P **Length of enrollment** 3 RSV seasons **Masking** Double-blind	To determine the effect of ribavirin therapy on (a) the course of the acute illness (b) bronchial responsiveness at 6 mos and (c) the frequency of lower respiratory tract symptoms in the yr following admission	**Inclusion criteria** • Previously fit infants • Moderately severe bronchiolitis • No high risk factors for severe disease • Bronchiolitis defined as: evidence of URI followed by development of lower respiratory tract involvement characterized by airways obstruction and widespread crepitations on auscultation **Exclusion criteria** None listed	**Number** 40 randomized, 35 completed study **Sex** Ribavirin: 43% male (9/21) Placebo: 47% male (9/19) **Mean age at enrollment in days (range)** Ribavirin: 93.7 (15 - 188) Placebo: 89.4 (16 - 266) **Mean gestational age** NR **Comorbidities** NR

Evidence Table 9. Ribavirin vs. Placebo (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 16)** Ribavirin 6 g in 180 ml H_20 by SPAG (Small Particle Aerosol Generator) over 18 hrs per day **Group B (n = 19)** Normal saline placebo Same protocol as Ribavirin group **Other treatment** Other treatments as needed	**Outcomes** **Primary outcomes** • Mean days in oxygen (ribavirin vs. placebo) – 3.36 vs. 2.52 • Change in clinical score between day 1 and day 0 (ribavirin vs. placebo) – - 0.83 vs. -1.05 • Change in oxygen saturation measured in air between day 1 and day 0 (ribavirin vs. placebo) – 2.05 vs. 0.57 • Days to discharge (ribavirin vs. placebo) – 5.58 vs. 3.95 • Days fit for discharge – 4.77 vs. 3.86 **Secondary outcomes** • Bronchial hyper - responsiveness • Admitted with lower respiratory tract (LRT) symptoms during first yr (ribavirin vs. placebo) – 2 (12.5%) vs. 3 (15.8%) • Bronchodilators during first yr (ribavirin vs. placebo) – 5 (31.3) vs. 8 (42.1%) • Inhaled steroids during first yr (ribavirin vs. placebo) – 2 (12.5%) vs. 1 (5.3%) • No LRT symptoms during first yr (ribavirin vs. placebo) – 4 (25%) vs. 5 (26.3%) • Readmission in first yr (ribavirin vs. placebo) – 2 (12.5%) vs. 3 (15.8%) **Subgroup analysis** None **Adverse events** • 1 patient died some months after discharge, death unrelated to ribavirin therapy	**Significant differences between study groups** • No (P = 0.41) • No (P = 0.83) • No (P = 0.15) • No (P = 0.11) • No (P = 0.37) • No • P values NR • P values NR • P values NR • P values NR • No (P = 0.46)	**Quality** Fair **Significant differences at baseline** None **Other comments** None

Evidence Table 9. Ribavirin vs. Placebo (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Guerguerian et al., 1999[79] **Setting** Canada, ICU **Followup** • Acute • Short term – length of hospitali-zation **Study design** RCT-P **Length of enrollment** March 94 to April 97 **Masking** Double-blind	To test the clinical effectiveness of ribavirin in previously well infants without underlying illnesses who require ventilatory support secondary to a first episode of RSV bronchiolitis	**Inclusion criteria** • First episode of bronchiolitis diagnosed with presence of tachypnea, chest retraction, prolonged expiratory time, pulmonary rales, or wheezing and hyperinflation on chest radiograph • Mechanical ventilation instituted for respiratory distress manifested by one or more of the following: – extreme fatigue, or impending respiratory arrest, or severe apnea if preceded by significant respiratory distress – uncompensated respiratory acidosis (pH < 7.30 and PCO_2 > 60 mm Hg – hypoxia (PaO_2 < 60 mm Hg or pulse oximetry saturation [SpO_2] < 93% with fraction of inspired oxygen [FIO_2] = 0.6) • Proven RSV etiology	**Number** 51 eligible, 42 enrolled, 41 used for intent-to-treat analysis **Sex** Placebo: 52% male (11/21) Ribavirin: 65% male (13/20) **Mean age at enrollment in days ± SD** Placebo: 62.5 ± 35.9 Ribavirin: 62.7 ± 30.9 **Mean gestational age** NR **Comorbidities** None

Evidence Table 9. Ribavirin vs. Placebo (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 20)** Aerosolized ribavirin 6 grams diluted w/ sterile water to a volume of 300 ml (20 mg/ml) **Group B (n = 21)** Saline placebo 300 ml saline (0.9%) Both administered by aerosol generator, over 18 hrs every 24 hrs for a maximum of 7 days or extubation **Other treatment** Sedation, paralysis, inhaled albuterol, steroids, antibiotics, chest physiotherapy as indicated	**Outcomes** **Primary outcome** • Mean length of mechanical ventilation in hrs ± SD (ribavirin vs. Placebo) – 102.16 ± 65.26 vs. 126.28 ± 78.72 **Secondary outcomes** • Length of aerosol therapy • Length of ICU stay • Length of oxygen therapy • Length of hospitalization **Subgroup analysis** No **Adverse events** • Acute respiratory distress syndrome leading to withdrawal from study (1 ribavirin pt.) • Right lobar pneumonia (1 placebo patient)	**Significant differences between study groups** • No (P = 0.29) • No (P = 0.31) • No (P = 0.42) • No (P = 0.44) • No (P = 0.32)	**Quality** Excellent **Significant differences at baseline** More preterm infants (< 37 wks gestation) in control group (P < 0.1) **Other comments** Length of ventilation among ribavirin pts reduces to 90.9 hrs when 1 patient. with ARDS is dropped from the analysis (P = 0.09)

Evidence Table 9. Ribavirin vs. Placebo (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Guerguerian et al., 1999[79] (continued)		**Exclusion criteria:** • Cyanotic congenital heart disease, congenital heart disease under medication or associated with pulmonary hypertension • Chronic respiratory disease e.g., BPD, CF, chronic aspiration, pulmonary hypoplasia, or neuromuscular disease • Central hypoventilation syndrome or altered airway protection • Primary or secondary immune deficiency • Chronic liver disease or renal failure • Previous treatment with ribavirin • Mechanical ventilation for > 24 hrs prior to the start of the aerosol treatment • Nosocomial acquired RSV infection (after 7 d of hospitalization) • Ribavarin administered for less than 18 hrs	

Evidence Table 9. Ribavirin vs. Placebo (continued)

Intervention	Outcome	Quality

Evidence Table 9. Ribavirin vs. Placebo (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Janai et al., 1993[80] **Setting** United States, inpatient **Followup** • Acute • Short term – 7 days after aerosol treatment **Study design** RCT-P **Masking** Double-blind **Length of enrollment** Winter of 1988 to 1989	To assess the effect of ribavirin on pulmonary function in infants with RSV bronchiolitis	**Inclusion criteria** • Clinical diagnosis of bronchiolitis • Presumptive rapid laboratory identification of RSV • Previously healthy • No ongoing cardiac, pulmonary, or immunologic disease • Products of normal gestation and delivery Bronchiolitis defined by presence of cough, dyspnea, expiratory wheezing, and hyperinflation on chest x-ray **Exclusion criteria** None listed	**Number** 26 randomized, 19 completed study **Sex** Placebo: 56% male (5/9) Ribavirin: 50% male (5/10) **Age at enrollment in weeks (interquartile range)** Placebo: 12 (6 to 16) Ribavirin: 14 (6 to 20) **Mean gestational age** NR **Comorbidities** None

Evidence Table 9. Ribavirin vs. Placebo (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 9)** Placebo 0.9% saline **Group B (n = 10)** Ribavirin 20mg/ml Both delivered by small particle aerosol generator (SPA6) for 18 hrs/day x 3 days (5 days for 1 infant) **Other treatment** Albuterol given prn to 8/9 placebo and 8/10 ribavirin patients 0.1 mg/kg/dose x 3 days Antibiotics and oxygen when indicated	**Outcomes** **Primary outcome** • Respiratory rate (numbers not reported) • Pulmonary function tests (compliance and resistance measured by sedating infant with 50 - 100 mg chloral hydrate on days 1, 2 and 7) **Subgroup analysis** None **Adverse events** None	**Significant differences between study groups** • No • Not significant except for change in compliance from day 1 to 7 (P = 0.05)	**Quality** Fair **Significant differences at baseline** None **Other comments** No clinically relevant outcomes

Evidence Table 9. Ribavirin vs. Placebo (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Rodriguez 1987[42] **Setting** United States, Inpatient **Followup** • Acute • Short term – 4 days after treatment **Study design** RCT-P **Length of enrollment** Dec 1983 - Mar 1984 **Masking** Double-blind	To assess the clinical and microbiologic effectiveness of ribavirin in the treatment of RSV disease	**Inclusion criteria** Admitted with acute ALRTI Proven RSV infection **Exclusion criteria** • Congenital heart disease	**Number** 30 patients enrolled **Sex** Placebo: 20% male (2/10) Ribavirin: 55% male (11/20) **Mean age at enrollment (mo.±SD)** Placebo: 3.2 ± 2.30 Ribavirin: 6.1 ± 7.1 **Mean gestational age (wks)** Placebo: 37.2 Ribavirin: 37.8 **Comorbidities** • Prematurity (20% in placebo grp, 15% in ribavirin grp) • Intraventricular hemorrhage (1 ribavirin pt) • BPD: (20% in placebo grp, 10% in ribavirin grp)

Evidence Table 9. Ribavirin vs. Placebo (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 10)** Placebo Distilled water **Group B (n = 20)** **Ribavirin** 6 mg in 300 ml sterile water Aerosols administered at the rate of 12.5 l/mins continuously (except for 1 - 3 period before daily nasal specimen collection or during nursing or medical procedures which required removing the infant from the tent) until considerable clinical improvement until 1+ on the analogue severity scale **Other treatment** O_2 as indicated	**Outcomes** **Primary outcome** • Mean severity of symptoms on analogue scale for Days 0, 1, 2, 3, and 4 after treatment (placebo vs. ribavirin) – day 0: 2.4 vs. 2.9 – day 1: 2.0 vs. 2.0 – day 2: 1.7 vs. 1.4 – day 3: 1.2 vs. 0.7 – day 4: 1.2 vs. 0.6 • Rate of change of symptom severity – day 0 to day 2 – day 0 to day 3 • Mean length of treatment in hrs (placebo vs. ribavirin) – 58.6 vs. 55.7 **Secondary outcomes** • Number of days treated • Number. of followup days in the hospital • Rectal temperatures • Days of fever from onset of illness • Days of fever from start of therapy • Rate of improvement in oxygen saturation from first day to last **Subgroup analysis** None **Adverse events** 2 deaths after treatment period (unrelated to intervention), 1 in placebo group (BPD and respiratory failure) and 1 in ribavirin grp (BPD, chronic hypoxemia, bronchiolitis, respiratory failure)	**Significant differences between study groups** • *P* values not reported • Yes – *P* = 0.007 – *P* = 0.001 • No (*P* = 0.63) • No (*P* = 0.46) • No (*P* = 0.09) • Ribavirin patients had significantly higher rectal temperatures on Day 1 (*P* = 0.02) and Day 2 (*P* = 0.01) but not thereafter • No (*P* = 0.54) • No (*P*=0.61) • Significant only for ribavirin grp (*P* = 0.02)	**Quality** Good **Significant differences at baseline** None **Other comments** None

Evidence Table 9. Ribavirin vs. Placebo (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Rodriguez et al., 1999[81] **Setting** Followup after hospital discharge of prior study[42] (Initial study Dec 1983 to February 1985) **Followup** Up to 6 yrs after RSV bronchiolitis **Study design** RCT-P (initial protocol) **Length of enrollment** Dec 1983 to Feb 1985 **Masking** Double-blind for initial study; not clear if masking maintained for followup	To determine any long-term differences in adverse effects and pulmonary function between infants with respiratory syncytial virus and lower respiratory tract infection who were treated with ribavirin and a control group	**Inclusion criteria** This study consists of the longitudinal evaluation of patients prospectively randomized to a ribavirin or a placebo control group. Initial therapeutic study • Infants = 1 month old • Admitted to the hospital with ALRTI • Proven RSV infection confirmed with indirect immunoflorescent antibody methods • Infants who were expected to stay 3 days or longer in the hospital **Exclusion criteria** • Congenital heart disease	**Number** 42 enrolled, 35 completed study (N varies by outcome) Initial study had N = 30 for this study. N for this study includes enrollees from next season **Sex** Ribavirin: 63% male (15/24) Placebo: 73% male (8/11) **Mean age at enrollment (mo)** Ribavirin: 4 Placebo: 3.3 **Mean gestational age (wks ± SE)** NR **Comorbidities** Patients with chronic pulmonary disease and prematurity included

Evidence Table 9. Ribavirin vs. Placebo (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 24)** Ribavirin **Group B (n = 11)** Placebo **Other treatment** NR	**Outcomes**	**Significant differences between study groups**	**Quality** Good **Significant differences at baseline** NR **Other comments**
	Primary outcome		
	• Mean score for presence of Pneumonia, RAD and wheezing during yrs 1 - 3 after RSV Bronchiolitis ± SD (ribavirin vs. placebo)	• No (P = 0.10)	
	– 16.02 ± 27.69 vs. 22.31 ± 27.69		
	• Mean score for presence of Pneumonia, RAD and wheezing during yrs 1 - 6 after RSV Bronchiolitis ± SD (ribavirin vs. placebo)	• No (P = 0.10)	
	– 16.08 ± 27.78 vs. 22.18 ± 27.78		
	–		
	• Number. with 2 or more wheezing episodes during yrs 1 - 6 (ribavirin vs. placebo)	• Yes (P = 0.04)	
	– 17% (4/24) vs. 55% (6/11)		
	Secondary outcomes		
	• PFTs measured on 6 placebo and 13 Ribavirin patients	• Placebo patients more likely to have moderate to severe findings compared to ribavirin group (P = 0.043)	
	• Methacholine challenge on 5 placebo and 7 ribavirin patients	• Results in favor of less severity in ribavirin group, significant only when weighted for disease severity without correction for small sample size	
	Subgroup analysis RSV status		
	Adverse events NR		

Evidence Table 9. Ribavirin vs. Placebo (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Taber et al., 1983[45] **Setting** United States, 2 hospitals Inpatient at baseline, not specified at followup **Followup** • Acute • Short term – 2 wks **Study Design** RCT-P **Length of enrollment** Dec 1981 to Feb 1982 **Masking** Partial blinding of observers	To examine the efficacy of ribavirin in the treatment of bronchiolitis associated with RSV infection in infants	**Inclusion criteria** • Hospitalization • Recent onset of acute lower respiratory infection consistent with bronchiolitis • RSV in nasal secretions **Exclusion criteria** All infants were full term and without cardiac and pulmonary disease. Unclear whether exclusion criteria or chance	**Number** 26 eligible and initiated study **Sex** Ribavirin: 33% male (4/12) Control: 71% male (10/14) **Mean age at enrollment in mo. ± SE** Ribavirin: 3.9 ± 3.3 Control: 3.7± 2.9 **Mean gestational age** NR **Comorbidities** None

Evidence Table 9. Ribavirin vs. Placebo (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 12)** Ribavirin by aerosol 0.8 mg/kg/hr for ~ 12 hrs/day up to 4 days **Group B (n = 14)** Control (saline aerosol) no additional details provided **Other treatment** Standard care, details not reported	**Outcomes** **Primary outcome** • Mean symptom score from 0 - 3+ on Day 0, 1, 2, and 3 (ribavirin vs. control) – Day 0 (Grp A= 14, Grp B=16): 2.0 vs. 2.0 – Day 1 (Grp A= 11, Grp B=12): 1.5 vs. 1.7 – Day 2 (Grp A= 9, Grp B=11): 1.0 vs. 1.3 – Day 3 (Grp A= 7, Grp B=10): 0.6 vs. 1.3 **Secondary outcomes** • Length of treatment • End of treatment to discharge • Total time, onset to discharge • RSV Titers in nasal secretions • RSV Neutralizing antibody response • Hematologic indices **Subgroup analysis** None **Adverse events** None	**Significant differences between study groups** • Significantly diff on day 3 alone (P = 0.044) • No • No • No • No • Yes (P = 0.045) • No	**Quality** Fair **Significant differences at baseline** Patients in control group had symptoms longer before beginning treatment, diff not statistically significant **Other comments** • No Intent-to-treat analysis • Only 17 of 26 patients remained for the one outcome that was significant • Results do not support conclusion

Evidence Table 10. Antibiotics vs. No Treatment or Other Antibiotics

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Friis et al., 1984[49] **Setting** Denmark, Inpatient **Followup** • Acute • Short term - 3 wks **Study design** RCT - No placebo **Length of enrollment** Dec 1979 to Nov 1982 **Masking** Open label	To assess the effect of routine administration of antibiotics in the treatment of viral pneumonia and bronchiolitis	**Inclusion criteria** • Children with pneumonia admitted to pediatric wards • Ill for less than one wk • No antibiotics before hospital admission **Exclusion criteria** • Chronic pulmonary or cardiac disease • Mental retardation • Oncologic diseases • Severe breathing difficulties or cyanosis • Oxygen treatment or artificial ventilation • Suspected septicemia	**Number** 136 eligible of which 61 had RSV (evidence table limited to RSV Subgroup) **Sex** Antibiotics: 65% male (47/72) Control: 67% male (44/66) **Median age at enrollment in mos** Antibiotics: 18 Control: 17.5 **Mean gestational age** NR **Comorbidities** None

Evidence Table 10. Antibiotics vs. No Treatment or Other Antibiotics (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 34)** Antibiotics If < 2 yrs, Ampicillin PO 100mg/kg/day TID x 6 days If > 2 yrs, V Penicillin 300000 IU TID x 6 days If > 2 yrs with penicillin allergy, erythromycin 30 - 50mg/kg/day TID x 6 days Treatment changed if strains were resistant (No details reported) **Group B (n = 27)** Control No therapy, 7 patients given antibiotics when they developed cyanosis, or bacterial complications, or fever lasting more than 4 days without viral infection diagnosed by IFA antibody test **Other treatment** NR	**Outcomes** **Primary outcome** • Mean duration of hospitalization in days ± SE (antibiotics vs. control for RSV subgroup) - 5.2 ± 0.3 vs. 5.4 ± 0.4 • 'Pulmonarily healthy' on day 3 (antibiotics vs. control for RSV subgroup) - 11 (32.4%) vs. 9 (33.3%) • 'Pulmonarily healthy' at discharge (antibiotics vs. control for RSV subgroup) - 25 (73.5%) vs. 24 (88.9%) • 'Pulmonarily healthy' after 3 wks (antibiotics vs. control for RSV subgroup) - 27 (79.4%) vs. 20 (74.1%) **Secondary outcomes** • Respiratory rate per mins measured at days 1, 2, 3 and discharge • Radiological findings on admission and after 3 wks **Adverse events** Fever, respiratory distress, coughing, otalgia, skin eruptions, GI symptoms, medical attention, antibiotics after day 10 for all patients, details NR for bronchiolitis group	**Significant differences between study groups** • No, *P* value NR • No, *P* value NR • No, *P* value NR • No, *P* value NR • No, *P* value NR	**Quality** Fair **Significant differences at baseline** NR **Other comments** • Neither patients nor investigators were blinded

Evidence Table 10. Antibiotics vs. No Treatment or Other Antibiotics (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Klein 1995[82] **Setting:** France, Belgium, Germany, South Africa; setting for enrollment NR **Followup** • Short term - end of treatment at Day 12 - 13 • Long term - days 20 - 30 **Study design** RCT non-placebo **Masking** Open label	To compare cefpodoxime proxetil with amoxicillin/clavanulate in the treatment of community - acquired acute febrile lower respiratory tract infections (14 patients with bronchiolitis were included)	**Inclusion criteria** • Age 3 mos to 10 yrs • Weight = 7 kg • Fever = 38°C • Suspected bacterial infection • Abnormal chest x-ray • Signs and symptoms of acute lower respiratory tract infection such as cough, tachypnea, wheezes (rhonchi) and crackles (rales) **Exclusion criteria** • Allergy to beta-lactams • Tuberculosis present or suspected • Bronchiectasis or congenital respiratory anomalies • Nosocomial pneumonia • Need for parenteral antibiotics • Antibiotic therapy within previous 48 hrs	**Number** 348 enrolled, 278 at Day 12 - 13, 233 at followup 19 with bronchiolitis **Sex** NR **Mean age at enrollment (yrs)** Grp A: 1.8 Grp B: 3.1 **Mean gestational age** NR **Comorbidities** NR

Evidence Table 10. Antibiotics vs. No Treatment or Other Antibiotics (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 234, n for bronchiolitis subgroup NR)** Cefpodoxime proxetil Scheduled dose: 40 mg BID if >7 to <15 kg 80 mg BID if =15 kg Actual dose: 5 to 12 mg/kg/day BID **Group B (n = 114, n for bronchiolitis subgroup NR)** Amoxicillin/clavanulate Scheduled dose: 125/31.25 mg TID if >7 to <15 kg 250/62.5 mg TID if =15 kg Actual dose: 25 to 53/6 to 13 mg/kg/day TID **Other treatment** Analgesics, antipyretics, bronchodilators, physiotherapy as needed	**Outcomes** **Primary outcome** • Clinical cure or improvement for bronchiolitis subgroup (%: Grp A vs. Grp B) - 90 (9/10) vs. 100 (4/4) **Adverse events** • Vomiting, viral disease, bronchospasm, diarrhea and rash for all patients (not reported for bronchiolitis subgroup) • 4 patients in 0 overall study group discontinued due to side effects	**Significant differences between study groups** • NR	**Quality** Poor **Significant differences at baseline** Grp A younger than Grp B, *P* = 0.03 **Other comments** • Patients with Bronchiolitis made up only 4% of patients in study • Loss to followup 20% without accounting for reasons • Outcomes for 14 out of 19 bronchiolitis patients, loss not explained

Evidence Table 11. RSVIG IV as Treatment for Bronchiolitis

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Rodriguez et al., 1997[25] **Setting** United States, Inpatient at baseline, telephone followup **Followup** • Acute • Short term - Monthly telephone calls • Long-term at 1 yr after intervention **Study design** RCT-P **Length of enrollment** 4 RSV seasons (yrs not stated) **Masking** Double-blind	To determine the safety and efficacy of RSVIG in the treatment of previously healthy children hospitalized with RSV infection	**Inclusion criteria** • Previously healthy • = 2 yrs of age • Hospitalized with bronchiolitis and/or pneumonia with nasal wash specimens positive for RSV • Acute lower respiratory symptoms of less than 4 days duration • Respiratory score of = 2.5 **Exclusion criteria** • Known or suspected cardiopulmonary disease • Premature birth with a gestational age < 32 wks • Immunodeficiency disease (including human immunodeficiency virus infection) • Known serum IgA deficiency • Renal failure • Previous reaction to blood products • Receipt of blood or blood products in the preceding 60 days • Established diagnosis of reactive airway disease • Apnea without evidence of LRI on presentation • Inability to establish an intravenous line after 4 attempts • Admitted for Ribavarin therapy	**Number** 101 eligible, 98 completed study **Sex** RSVIG: 48% male (22/46) Placebo 50% male (26/52) **Mean age at enrollment (yr.± SD)** RSVIG: 0.20 ± 0.03 Placebo: 0.19 ± 0.03 **Mean gestational age (wk.± SD)** RSVIG: 38.0 ± 0.4 Placebo: 38.2 ± 0.4 **Comorbidities** Patients on ventilators: RSVIG: 12/46 (26%) Placebo: 19/52 (37%)

Evidence Table 11. RSVIG IV as Treatment for Bronchiolitis (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 46)** RSVIG 30ml/kg (1500 mg/kg) IV infusion x 1 dose **Group B (n = 52)** Placebo IV Albumin 0.5%, same volume as intervention **Other treatment** Ribavirin therapy, IV fluids, nebulization treatments, steroids or antibiotics, supplemental oxygen, mechanical ventilation	**Outcomes**	**Significant differences between study groups**	**Quality** Good **Significant differences at baseline** • RSVIG grp more likely to have = 85% study entry O_2 saturation level (46% vs. 29%, *P* = 0.07) • Placebo grp more likely to need ICU care and mechanical ventilation (*P* value NR) **Other comments** • If pt received 25% of infusion, was eligible for adverse outcomes reporting and if 75% of infusion then also for all other outcomes
	Primary outcome • Mean duration of hospitalization in days ± SE (RSVIG vs. Placebo) - 4.58 ± 0.4 vs. 5.52 ± 0.69 • Mean duration of stay in ICU in days ± SE (RSVIG vs. placebo) - 3.92 ± 0.58 (n = 25) vs. 6.60 ± 1.31 (n = 33)	• No (*P* = 0.24) • No (*P* = 0.06)	
	Secondary outcomes • Duration of mechanical ventilation • Duration of oxygen therapy • Use of ribavirin • Supplemental oxygen • RSV neutralizing antibody • Proportion of cultures for RSV • Hospitalization of LRI in subsequent season • Hospitalization of RSV LRI in subsequent season	• No (*P* = 0.45) • No • No • No • No • No • NR • NR	
	Subgroup analysis • Severity of illness - Among subgroup with more severe disease (respiratory scores = 3.0), lower duration of hospitalization in RSVIG grp than placebo • ICU stay at entry - Lower duration of hospitalization in RSVIG grp than placebo	• *P* values not provided, n too small • *P* values not provided, n too small	
	Adverse events • Benign nocturnal myoclonus not related to RSVIG (1 RSVIG pt.) • Cardiopulmonary findings (6 RSVIG pts, 8 placebo pts)		

Evidence Table 11. RSVIG IV as Treatment for Bronchiolitis (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Rodriguez et al., 1997[41] **Year** 1997 **Setting:** United States, Multi-center, Inpatient **Followup** • Acute • Short term - Monthly telephone calls • Long-term at 1 yr after intervention **Study design** RCT-P **Masking** Double-blind	To evaluate the efficacy of intravenous RSVIG to treat severe RSV in high risk infants	**Inclusion criteria** • High risk infants and children 2 yrs and younger • Hospitalized for RSV, bronchiolitis and/or pneumonia • Positive for RSV antigens High-risk criteria definitions: - severe BPD - other serious chronic lung disease - congenital heart disease - preterm infants <6 months old and <32 wks gestation **Exclusion criteria** • Poorly controlled congestive heart failure before RSV illness • Renal failure • Ventilator dependency before RSV illness • Life expectancy< 6 months from study onset • Treatment with ribavirin before enrollment • Previous adverse reaction to blood products • Known IgA or other immunodeficiency • Enrollment in concurrent RSVIG study • Cystic fibrosis • Asthma • Reactive airway disease w/o BPD • Apnea w/o LRI • Admission for ribavirin therapy	**Number** 107 enrolled, 102 received adequate dose, 96 at 8 wk followup, 98 at 1 yr followup **Sex** RSVIG: 45% male (23/51) Placebo: 57% male (29/51) **Mean age at enrollment (yr.± SE)** RSVIG: 0.55 ± 0.07 Placebo: 0.58 ± 0.06 **Mean gestational age (wk.± SE)** RSVIG: 31.0 ± 0.8 Placebo: 30.7 ± 0.7 **Comorbidities** • Groups balanced at entry for BPD, congenital heart disease and prematurity. • History of LRI significantly more frequent in placebo group (37% for placebo vs. 18% for RSVIG)

Evidence Table 11. RSVIG IV as Treatment for Bronchiolitis (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 51)** RSVIG 30 mL/kg (1.5 mg/kg) IV x 1 dose over 12 hrs **Group B (n = 53)** Placebo 0.15 mg/kg albumin (identically appearing solution and schedule) **Other treatment** Supplemental oxygen, mechanical ventilation, ribavirin therapy	**Outcomes**	**Significant differences between study groups**	**Quality** Excellent **Significant differences at baseline** RSVIG group had more severe disease than placebo group: - ICU admission: 47% vs. 28% (*P* = 0.03) - Mechanical ventilation: 31% vs. 18% (*P* = 0.01) - Mean respiratory scores of 4 - 5: 45% vs. 29% (*P* = 0.38) **Other comments**
	Primary outcome		
	• Mean duration of hospitalization in days ± SE (RSVIG vs. placebo)	• No (*P* = 0.73)	
	- 8.41± 0.97 vs. 8.89 ± 0.99		
	• Mean duration of ICU stay in days ± SE (RSVIG vs. placebo)	• No (*P* = 0.90)	
	- 9.77± 1.66 (n = 31) vs. 10.27 ± 1.81 (n = 18)		
	• Development of RSV in hospitalized patients during subsequent respiratory season	• No (*P* value NR)	
	- 3/48 (6%) vs. 3/50 (6%)		
	• Readmission during subsequent respiratory season(RSVIG vs. placebo)	• No (*P* value NR)	
	- 5/48 (10%) vs. 6/50 (12%)		
	Secondary outcomes		
	• Duration of mechanical ventilation	• No	
	• Requirement for supplemental oxygen during hospitalization	• No	
	• Change in respiratory scores 24, 48, 72 and 96 hrs after infusion	• No	
	• Bronchodilator use	• No	
	• Ribavirin use	• No	
	• Steroid use	• No	
	Subgroup analysis		
	• Underlying diagnosis	• No	
	• Gestational age, year, center	• No	
	• Respiratory score	• No	
	• ICU stay at entry	• No	
	Adverse events		
	• RSVIG		
	- 22 events in 16 patients		
	- 16/22 possibly drug - related		
	• Placebo		
	- 11 events in 10 patients		
	- 8/11 events possibly drug - related		

Evidence Table 12. Other Miscellaneous Treatments for Bronchiolitis

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Chipps et al., 1993[47] **Setting** United States, Multi-center, Inpatient **Followup** None **Study design** RCT-P **Length of enrollment** Winters of 1989 to 1990 and 1990 to 1991 **Masking** Double-blind	To test whether the treatment of RSV bronchiolitis with alpha-2A-interferon (IFN) results in decreased symptoms and duration of illness	**Inclusion criteria** • < 24 mos of age • Lower respiratory disease caused by RSV (increased work of breathing, elevated respiratory rate, rales and/or wheezing) • Supplemental oxygen needed to maintain O_2 saturation > 92% **Exclusion criteria** • Cyanotic congenital heart disease • Underlying chronic disease	**Number** 22 completed study **Sex** NR **Age at enrollment** NR **Mean gestational age** NR **Comorbidities** Patients on ventilators: 6

Evidence Table 12. Other Miscellaneous Treatments for Bronchiolitis (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 11)** IFN 70,000 units/kg/day IM q x 5 days **Group B (n = 11)** Placebo 0.9% saline in similar volume IM **Other treatment** Inhaled beta-agonists, oxygen, antibiotics when indicated and fluids for hydration	**Outcomes** **Primary outcomes** • Total symptom score - wheezing - muscle retractions - accessory muscle use • Number of day of O_2 therapy to maintain O_2 > 92% **Secondary outcomes** • Respiratory rate • Pulse rate • ELISA assays for RSV antigens • RSV shedding in nasal secretions **Subgroup analysis** None **Adverse events** None	**Significant differences between study groups** • No (P > 0.05) • No (P values NR) • No (P > 0.05) • No (P > 0.05) • No (P values NR) • No (P values NR)	**Quality** Good **Significant differences at baseline** • Significant differences in baseline symptom scores suggesting failure of randomi - zation • Mechanical ventilation for 4 IFN patients vs. 2 placebo patients **Other comments** • Power is too low to detect differences in scores between study groups (study was halted because of concerns about cardiotoxicity in other studies, although none noted in this study) • Dose possibly too low to produce therapeutic effect

Evidence Table 12. Other Miscellaneous Treatments for Bronchiolitis (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Hollman et al., 1998[84] **Setting** United States, Intensive care unit **Followup** Acute **Study design** RCT-C (not all patients randomized) **Length of enrollment** NR **Masking** Double-blind	To determine the efficacy of a helium-oxygen mixture in children admitted to the pediatric intensive care unit with acute respiratory syncytial virus (RSV) bronchiolitis	**Inclusion criteria** • Positive for RSV • Signs of lower respiratory tract disease **Exclusion criteria** • FIO_2 > 0.50 requirement • Helium concentrations < 50% • Intubated • Signs of upper airway obstruction	**Number** 21 eligible, 3 excluded for technical reasons, 18 studied, 13 randomized **Sex** NR **Median age** 2.5 mos (3 wks - 24 mos) **Mean gestational age** NR **Comorbidities** Clinical asthma: 12 Underlying cardiac disease: 5 History of laryngomalacia: 1 Treacher Collins syndrome: 1

Evidence Table 12. Other Miscellaneous Treatments for Bronchiolitis (continued)

Intervention	Outcome		Quality
Intervention For randomized patients (n = 13): **Group A (n = 6)** Helium-oxygen mixture, followed by air-oxygen mixture, each for 20 mins **Group B (n = 7)** Air-oxygen mixture, followed by helium-oxygen mixture, each for 20 mins For non - randomized patients (Clinical Asthma score ≥ 6) (n = 5): Helium-oxygen mixture **Other treatment** Nebulized albuterol (17/18)	**Outcomes** **Primary outcome** • Mean change in Clinical Asthma scores ± SE, compared with baseline - Helium-oxygen mixture: 0.46 ± 0.18 - Air-oxygen mixture: 0.04 (SE not provided) **Secondary outcomes** • Mean heart rate • Respiratory rate **Adverse events** Mechanical ventilation, intubation and balloon angioplasty in 1 patient with coarctation of the aorta	**Significant differences between study groups** • Significant only for helium-oxygen mixture - $P < 0.05$ - Not significant, *P* value NR • No • No	**Quality** Fair **Significant differences at baseline** NR **Other comments** None

Evidence Table 12. Other Miscellaneous Treatments for Bronchiolitis (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author: Kong et al., 1993[51] **Setting:** China, Inpatient **Followup** • Acute • Short term **Study design** RCT-AT **Length of enrollment** 1988 - 1989 **Masking** Single-blind trial (investigator blind to treatment)	To test the hypothesis that Shuang Huang Lian is a safe and effective treatment of acute bronchiolitis	**Inclusion criteria:** Children admitted with lower respiratory tract disease and serological evidence of RSV **Exclusion criteria:** Underlying illness such as congenital heart disease	**Number** 96 enrolled, 96 completed study **Sex** Grp A: 68.8% male (22/32) Grp B: 67.6% male (23/34) Grp C: 63.3% male (19/30) **Median age at enrollment in months (range)** Grp A: 12 (3 - 48) Grp B: 12 (2 - 36) Grp C: 10 (2 - 48) **Mean gestational age** NR **Comorbidities** None, previous history of LRI not reported

Evidence Table 12. Other Miscellaneous Treatments for Bronchiolitis (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 32)** Shuang Huang Lian <6 mo.: 20 ml IV 7 - 36 mo.:40 ml IV 36+ mo.: 60 ml IV qd x 7 d. **Group B (n = 34)** Shuang Huang Lian plus antibiotics Shuang Huang Lian: same dose and schedule as Group A, qd x 7 d. Antibiotics: Lincomycin IV 30 mg/kg/day or Cephazolin IV 100mg/kg/day, qd x 7 d. **Group C (n = 30)** Antibiotics, same dose and schedule as Group B **Other treatment** Aspirin as indicated	**Outcomes** **Primary outcomes** • Mean days of wheezing (95% C.I.) (n = 87) - Grp A: 4.2 (3.7 - 4.9) - Grp B: 4.0 (3.4 - 4.6) - Grp C: 6.1 (5.2 - 7.3) • Mean days of any sign or symptom (C.I.) (n = 96) - Grp A: 6.4 (5.6 - 7.3) - Grp B: 6.0 (5.0 - 7.1) - Grp C: 8.6 (7.5 - 9.8) • Hospital stay (C.I.) (n = 96) - Grp A: 7.8 (7.0 - 8.6) - Grp B: 7.0 (6.3 - 7.8) - Grp C: 9.8 (8.8 - 11.0) **Secondary outcomes** • Cough • Fever • Chest wheezes • Chest crackles **Subgroup analysis** None **Adverse events** None observed	**Significant differences between study groups** • Yes for groups AB combined vs. C ($P < 0.01$) • Yes for groups AB combined vs. C ($P < 0.01$) • Yes for groups AB combined vs. C ($P < 0.01$) • Yes for groups AB combined vs. C ($P < 0.01$) • No • Yes for groups AB combined vs. C ($P < 0.01$) • Yes for groups AB combined vs. C ($P < 0.01$)	**Quality** Fair **Significant differences at baseline** None **Other comments:** • No rationale provided for the use of two different antibiotics • 7 day stay in hospital impractical in Western context • Statistical tests compared grp A and B compared with grp C

Evidence Table 12. Other Miscellaneous Treatments for Bronchiolitis (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Luchetti et al., 1998[39] **Setting** Italy, intensive care unit **Followup** Acute **Study Design** RCT non-placebo **Length of enrollment** Winters of 1995 - 1996 and 1996 - 1997 **Masking** Cannot determine	To assess the effect of surfactant treatment on gas exchange, PIP, duration of mechanical ventilation and ICU stay in children with severe bronchiolitis	**Inclusion criteria** • 20 days - 2.5 yrs • Severe bronchiolitis requiring mechanical ventilation • On CPPV for 24 hrs without significant improvement • PIP > 35 cm H_2O after 24 hrs of CPPV **Exclusion criteria** None listed	**Number** 20 completed study **Sex** Surfactant: 60% male (6/10) Control: 50% male (5/10) **Mean age at enrollment (mo ± SE)** Surfactant: 10.4 ± 1.8 Control: 11.2 ± 2.0 **Mean gestational age (wk ± SE)** NR **Comorbidities** None reported

Evidence Table 12. Other Miscellaneous Treatments for Bronchiolitis (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 10)** **CPPV + porcine-derived surfactant** Surfactant 50 mg/kg instilled into trachea in 2 to 3 doses (details NR) CPPV • Postural drainage and chest clapping performed between doses • Ventilatory management same for 2 groups • Respiratory rate 20 - 40 breaths/min based on age of child • Tidal vol. 10 ml/kg. • PEEP always used increasing from 5 - 10 cm H_2O over 12 - 24 hrs • FiO_2 as low as possible. • Children sedated and paralyzed during surfactant administration. • CPPV discontinued when clinical and x-ray signs of disease disappeared and blood gas values as follows: • PaO_2 = 12.6 KPa with FiO_2 =0.3 • $PaCO_2$ = 5.6 KPa **Group B (n = 10)** CPPV **Other treatment** • All patients received O_2, ß2 - agonists and antibiotics. • Aminophylline and systematic corticosteroids for some patients, no significant differences across study groups	**Outcomes** **Primary outcome** • Mean duration of ICU stay in days ± SD (CPPV + surfactant vs. CPPV): - 10.1 ± 1.2 vs. 15.7 ± 1.5 • Mean duration of CPPV in days ± SD (CPPV + surfactant vs. CPPV): - 4.4 ± 0.4 vs. 8.9 ± 1.0 **Secondary outcomes** • Mean PaO_2/FiO_2 ratio ± SD (CPPV + surfactant vs. CPPV) at: - 1 hr: 25.7 ± 2.2 vs. 19.0 ± 1.8 - 3 hr: 23.7 ± 1.9 vs. 18.3 ± 1.9 - 12 hr: 30.0 ± 2.5 vs. 19.7 ± 1.9 - 24 hr: 30.8 ± 2.7 vs. 19.4 ± 1.6 • $PaCO_2$ at 12 and 24 hrs • Peak inspiratory rate at 3, 12 and 24 hrs **Subgroup analysis** None **Adverse events** None	**Significant differences between study groups** • Yes ($P < 0.05$) • Yes ($P < 0.05$) • Significant for all time periods - ($P < 0.05$) - ($P < 0.05$) - ($P < 0.01$) - ($P < 0.01$) • Yes (all $P < 0.05$) • Yes (all $P < 0.05$)	**Quality** Fair **Significant differences at baseline** None **Other comments** Masking of investigators not reported

Evidence Table 12. Other Miscellaneous Treatments for Bronchiolitis (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Van Bever et al., 1995[85] **Setting** Belgium, emergency department **Followup** None **Study design** RCT-P **Length of enrollment** NR **Masking** Double-blind	To study the effects of aerosolized furosemide on: • acutely wheezing babies and • intermittently wheezing babies Study also enrolled a second population of "intermittently wheezing babies" using PFTs as primary outcome. These data were excluded from this evidence table	**Inclusion criteria** • Initial attack of acute bronchiolitis for Part A inclusion **Exclusion criteria** • Previous bronchodilator therapy • Severe dyspnea • Lethargy • Underlying cardiorespiratory disease • Underlying metabolic disease • Underlying liver disease • Underlying renal disease • Premature babies with bronchopulmonary disease	**Number** 48 total enrolled, 28 in Part A (acute wheezing), 20 in Part B (intermittent wheezing) **Sex** Part A: 61% male **Mean age at enrollment (mo ± SE)** Part A: 6.1± 3.2 mos **Mean gestational age** NR **Comorbidities** None for Part A

Evidence Table 12. Other Miscellaneous Treatments for Bronchiolitis (continued)

Intervention	Outcome		Quality
Intervention **Part A (n = 28)** Nebulized furosemide (N not reported) 10 mg over 10 mins, with nebulizer flow at 6 to 8 L/min Placebo (N not reported) 4 ml saline over 10 mins **Other treatment** NR	**Outcomes** **Primary outcome** • Log of total clinical score ± SD at baseline, 15 mins and 30 mins after therapy for Part A (mean ± SD for Furosemide vs. placebo) - Baseline: 0.72 ± 0.16 vs. 0.71 ± 0.19 - 15 mins: 0.67 ± 0.19 vs. 0.62 ± 0.27 - 30 mins: 0.59 ± 0.28 vs. 0.56 ± 0.24 **Subgroup analysis** None **Adverse events** NR	**Significant differences between study groups** • No (*P* values NR)	**Quality** Good **Significant differences at baseline** None **Other comments** None

Evidence Table 12. Other Miscellaneous Treatments for Bronchiolitis (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Nasr et al., 2001[40] **Setting** United States, two-center study, inpatient **Followup** Acute **Study design** RCT-P **Length of enrollment** Feb 1996 - Mar 1998 **Masking** Double-blind	To test whether therapy with recombinant human deoxyribonuclease (rhDNase) may result in shorter length of hospitalization, improved clinical scores, and improved CXR's in hospitalized infants with RSV infection as a result of its mucolytic properties	**Inclusion criteria** • = 2 yrs of age • Previously healthy full-term neonates • Proven RSV infection **Exclusion criteria** None listed	**Number** 86 enrolled, 75 completed study **Sex** Placebo: 63% male (22/35) rhDNase: 63% male (25/40) **Mean age at enrollment (mo.± SD)** Placebo: 4.53 (4.56) rhDNase: 5.43 (6.26) **Mean gestational age** NR **Comorbidities** Patients on ventilators: 6

Evidence Table 12. Other Miscellaneous Treatments for Bronchiolitis (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 35)** Placebo 2.5 mL excipient once daily up to 5 days **Group B (n = 40)** rhDNase 2.5 mg (1mg/mL) in 2.5 mL of excipient once daily up to 5 days, nebulized using tight - fitting face mask **Other treatment** Nebulized albuterol as per institutional RSV protocol	**Outcomes** **Primary outcome** • Mean duration of hospitalization in days ± SD (Placebo vs. rhDNase): - 3.34 ± 2.3 vs. 3.33 ± 2.00 **Secondary outcomes** • Mean change between hospital admission and discharge ± SD (Placebo vs. rhDNase) for - Respiratory score - Wheezing score - Retraction score - CXR score: - 0.60 ± 1.38 vs. 0.46 ± 1.06 **Adverse events** None	**Significant differences between study groups** • No (P = 0.97) • No significant differences for any outcome other than CXR score (P < 0.001)	**Quality** Good **Significant differences at baseline** Trends suggest rhDNase grp more ill than placebo grp, no significant differences **Other comments** None

Evidence Table 13. RSVIG IV vs. Placebo or Standard Care to Prevent RSV Bronchiolitis

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Groothuis et al., 1993[87] **Setting:** United States, multi-center, outpatient at baseline, telephone survey at followup **Followup** • Long-term - monthly for 5 months during initial RSV season - subsequent RSV season **Study design** RCT non-placebo **Masking** Non-blinded team responsible for enrollment and well-baby exams and exams at the time of infusion; blinded team responsible for weekly followup and evaluation of all respiratory illnesses	To test whether RSV infection could be attenuated or prevented in high-risk children by monthly infusions of RSVIG during the RSV season	**Inclusion criteria** • Less than 48 mos old at beginning of study • Had congenital heart disease or cardiomyopathy, bronchopulmonary dysplasia, or premature delivery (= 35 wks) and a chronological age of less than 6 mos **Exclusion criteria** • Immunodeficiency • Poorly controlled heart or renal failure • Dependence on a ventilator • Expected survival of less than 6 mos	**Number** 249 enrolled, data on 249 in first season study, 210 contacted for followup in subsequent season **Sex** High-dose RSVIG: 57% male (46/81) Low - dose RSVIG 49% male (39/79) Control: 63% (56/89) **Mean age at enrollment (mo.± SE)** High-dose RSVIG: 8.4 ± 6.1 Low - dose RSVIG: 7.6 ± 6.1 Control: 8.4 ± 7.2 **Mean gestational age (wk.± SE)** NR **Comorbidities** See inclusion criteria

Evidence Table 13. RSVIG IV vs. Placebo or Standard Care to Prevent RSV Bronchiolitis (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 81)** High-dose RSVIG 750 mg/kg IV per month **Group B (n = 79)** Low - dose RSVIG 150 mg/kg IV per month **Group C (n = 89)** Control Standard care, no RSVIG **Other treatment** Routine care as needed, including ribavirin, hospitalization or ICU admission, mechanical ventilation	**Outcomes** **Primary outcome** • RSV-related acute respiratory disease - Grp A: 19 - Grp B: 16 - Grp C: 29 • Non-RSV acute respiratory disease - Grp A: 65 - Grp B: 77 - Grp C: 72 • RSV-related lower respiratory tract infections (respiratory score of 2+) - Grp A: 7 - Grp B: 13 - Grp C: 20 • Non-RSV lower respiratory tract infections (respiratory score of 2+) - Grp A: 14 - Grp B: 22 - Grp C: 24 • Moderate to severe RSV-related lower respiratory tract infections (respiratory score of 3+) - Grp A: 3 - Grp B: 5 - Grp C: 12 • Moderate to severe Non-RSV lower respiratory tract infections (respiratory score of 3+) - Grp A: 2 - Grp B: 4 - Grp C: 5	**Significant differences between study groups** • No - Grp A vs. Grp C: *P* = 0.19 - Grp B vs. Grp C: *P* = 0.08 • No - Grp A vs. Grp C: *P* = 0.99 - Grp B vs. Grp C: *P* = 0.49 • Significant for some comparisons - Grp A vs. Grp C: *P* = 0.01 - Grp B vs. Grp C: *P* = 0.35 • No - Grp A vs. Grp C: *P* = 0.20 - Grp B vs. Grp C: *P* = 0.79 • Significant for some comparisons - Grp A vs. Grp C: *P* = 0.03 - Grp B vs. Grp C: *P* = 0.13 • No - Grp A vs. Grp C: *P* = 0.45 - Grp B vs. Grp C: *P* = 0.99	**Quality** Good **Significant differences at baseline** History of hospitalization for proven RSV illness more common among high-dose RSVIG group (*P* = 0.05) **Other comments** Benefit statistics tend to be greatest for preterm infants and infants with BPD but supporting data were not reported

Evidence Table 13. RSVIG IV vs. Placebo or Standard Care to Prevent RSV Bronchiolitis (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Groothuis et al., 1993[87] (continued)			

Evidence Table 13. RSVIG IV vs. Placebo or Standard Care to Prevent RSV Bronchiolitis (continued)

Intervention	Outcome		Quality
	Secondary Outcomes		
	• Hospitalizations - Grp A: 6 - Grp B: 10 - Grp C:18	• Significant for some comparisons - Grp A vs. Grp C: *P* = 0.02 - Grp B vs. Grp C: *P* = 0.19	
	• Hospital days - Grp A: 43 - Grp B: 63 - Grp C: 128	• Significant for some comparisons - Grp A vs. Grp C: *P* = 0.02 - Grp B vs. Grp C: *P* = 0.12	
	• Admission to ICU - Grp A: 1 - Grp B: 0 - Grp C: 6	• Significant for some comparisons - Grp A vs. Grp C: *P* = 0.12 - Grp B vs. Grp C: *P* = 0.03	
	• Days in ICU - Grp A: 1 - Grp B: 0 - Grp C: 34	• Yes - Grp A vs. Grp C: *P* = 0.05 - Grp B vs. Grp C: *P* = 0.03	
	Adverse events 19 in 580 infusions (3%) • Fluid overload (5 pts) • Oxygen desaturation (8 pts) • Fever • Death (unrelated to intervention) • At least 1 problem with IV success in 60% of children		

Evidence Table 13. RSVIG IV vs. Placebo or Standard Care to Prevent RSV Bronchiolitis (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Groothuis et al., 1995[86] **Setting** United States, multicenter, outpatient at baseline, telephone survey at followup **Followup** • (From Groothuis 1993,[87] details NR in this study) • Long-term - monthly for 5 months during initial RSV season - subsequent RSV season **Study design** **Study design** • (From Groothuis 1993,[87] details NR in this study) RCT non-placebo **Length of enrollment** 3 RSV seasons	Subgroup analysis study of original trial to evaluate the safety and efficacy of RSVIG in the prevention of severe RSV lower respiratory tract infection in infants born prematurely, with or without BPD	**Inclusion criteria** • Infants enrolled in prophylaxis trial by Groothuis and colleagues • = 35 wks gestational age • With or without BPD **Exclusion criteria** • Congenital heart disease	**Number** 249 enrolled, data on 249 in first season study, 210 contacted for followup in subsequent season in original study, 116 (58 high-dose RSVIG and 58 control) in this analysis out of a total 162 preterm children **Sex** NR **Mean age at enrollment** NR **Mean gestational age** NR **Comorbidities** All preterm with BPD: 102 All preterm without BPD: 60 Details NR for subset in this analysis of high-dose RSVIG vs. control (n = 116)

Evidence Table 13. RSVIG IV vs. Placebo or Standard Care to Prevent RSV Bronchiolitis (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 58)** RSVIG High-dose RSVIG 750 mg/kg IV per month for a total of 3 to 5 doses during RSV season **Group B (n = 58)** Control Standard care, no RSVIG **Other treatment** (From Groothuis 1993, details NR in this study) Routine care as needed, including ribavirin, hospitalization or ICU admission, mechanical ventilation **Masking** • (From Groothuis 1993,[87] details NR in this study) Unblinded team responsible for enrollment and well-baby exams and exams at the time of infusion • Blinded team responsible for weekly followup and evaluation of all respiratory illnesses	**Outcomes** **Primary outcome** • Incidence of RSV LRTI (score = 2) (RSVIG vs. control) - 4 (6.9%) vs. 14 (24.1%) • Incidence of moderate to severe RSV LRTI (respiratory score = 3) (RSVIG vs. control) - 1 (1.7%) vs. 10 (17.2%) • Hospitalization for RSV infection (RSVIG vs. control) - 4 (6.9%) vs. 13 (22.4%) • Mean duration of hospitalization in days (RSVIG vs. control) - 31 vs. 83 • Mean duration in ICU in days (RSVIG vs. control) - 1 vs. 30 • Mean worst respiratory score with RSV ± SD - 1.5 ± 0.26 vs. 2.63 ± 0.31 **Subgroup analysis** None **Adverse events** 5% of all RSVIG infusions resulted in acute reactions, details NR in this study	**Significant differences between study groups** • Yes (*P* = 001) • Yes (*P* = 0.006) • Yes (*P* = 0.02) • No (*P* = 0.06) • Yes (*P* = 0.05) • Yes (*P* = 0.02)	**Quality** Good **Significant differences at baseline** History of hospitalization for proven RSV illness more common among high-dose RSVIG group (*P* = 0.05) **Other comments** None

Evidence Table 13. RSVIG IV vs. Placebo or Standard Care to Prevent RSV Bronchiolitis (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Simoes et al., 1998[88] **Setting** United States, multi-center **Followup** Short term **Study Design** RCT non-placebo **Length of enrollment** 3 RSV seasons from 1992 to 1995 **Masking** Enrollment and treatment team non-blinded, weekly surveillance and clinical evaluation team blinded	To examine the effectiveness of Respiratory syncytial virus immune globulin administered intravenously in reducing hospitalization for treatment of RSV in children with congenital heart disease	**Inclusion criteria** • < 48 mos of age • Congenital heart disease or cardiomyopathy **Exclusion criteria** • Immunodeficiency disease • RSV infection immediately before study entry • Previous reaction to blood products • Poor venous access • Renal failure • Ventilator dependency • Heart transplant candidates • Life expectancy < 6 mos	**Number** 425 enrolled, 416 completed study, no explanation provided for dropouts **Sex** RSVIG: 53% male (108/202) Control: 53% male (114/214) **Mean age in mo ± SD** RSVIG: 9.3 ± 9.4 Control:10.7 ± 10.1 **Mean gestational age in wks ± SD** RSVIG: 38.6 ± 2.2 Control:38.3 ± 2.9 **Comorbidities** See inclusion criteria

Evidence Table 13. RSVIG IV vs. Placebo or Standard Care to Prevent RSV Bronchiolitis (continued)

Intervention	Outcome		Quality
Intervention	**Outcomes**	**Significant differences between groups**	**Quality**
	Primary outcomes		Good
Group A (n = 202)			
RSVIG IV	• Acute respiratory illness (RSVIG IV vs. control)	• Yes (*P* = 0.02)	**Significant differences at baseline**
750 mg/kg (15ml/kg) IV of q month during RSV season	- 73% vs. 82%		• More children with tetralogy of Fallot or tricuspid atresia in RSVIG IV group
Group B (n = 214)	• RSV URI (RSVIG IV vs. control)	• No (*P* = 0.97)	• More children with left-to-right shunt in control group)
Control	- 6% vs. 7%		
	• RSV LRI (RSVIG IV vs. control)	• No (*P* = 0.26)	
Other interventions	- 19% vs. 24%		
Not reported	• All LRI associated hospitalizations (RSVIG IV vs. control)	• Yes (*P* = 0.02)	
	- 17% vs. 27%		
	• RSV LRI associated hospitalizations (RSVIG IV vs. control)	• No (*P* = 0.16)	
	- 10% vs. 15%		
	• Non-RSV LRI associated hospitalizations (RSVIG IV vs. control)	• No (*P* = 0.06)	
	- 6% vs. 12%		
	• RSV-LRI score = 3 (RSVIG IV vs. control)	• No (*P* = 0.36)	**Other comments**
	- 5% vs. 7%		None
	Secondary outcomes		
	• Admission to ICU for RSV LRI	• No	
	• Mechanical ventilator for RSV LRI	• No	
	• RSV hospital days/100 children	• No	
	• RSV hospital days with a score = 3/100 children	• No	
	• RSV ICU days/100 children	• No	
	• RSV mechanical ventilation/100 children	• No	

Evidence Table 13. RSVIG IV vs. Placebo or Standard Care to Prevent RSV Bronchiolitis (continued)

Study Characteristics	Stated objective	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Simoes et al., 1998[88] (continued)			

Evidence Table 13. RSVIG IV vs. Placebo or Standard Care to Prevent RSV Bronchiolitis (continued)

Intervention	Outcome		Quality
(continued)	**Subgroup analysis** RSV hospitalization by age and cardiac subgroup • Age: - < 6 months vs. = 6 months • Cardiac subgroup - Subgroup 1: biventricular heart without shunts - Subgroup 2: biventricular heart with right-to-left shunt - Subgroup 3: biventricular heart with left-to-right shunt - Subgroup 4: single ventricle or hypoplastic left heart	• Significant for all cardiac subgroups for age < 6 mos (P = 0.02), not significant for age = 6 mos (P = 0.74)	
	Adverse events Several listed	• Significantly greater for treatment groups for cardiac surgery associated adverse events other than death	

Evidence Table 13. RSVIG IV vs. Placebo or Standard Care to Prevent RSV Bronchiolitis (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author The PREVENT Study Group 1997[89] **Setting** United States, multi-center, outpatient **Followup** Long-term **Study design** RCT-P **Length of enrollment** 1994 - 1995 RSV season **Masking** Double-blinding	To determine the safety and efficacy of RSVIG IV prophylaxis for reducing the rate of RSV hospitalization among children with BPD and/or a history of prematurity	**Inclusion criteria** • ≤ 24 months old with BPD (diagnosed by a neonatologist or pulmonologist) and a requirement for supplemental oxygen within the past 6 months or • <6 mos old and premature at birth (35 wks gestation or less) **Exclusion criteria** • Required hospitalization at time of randomization (unless discharge was anticipated within 30 days) • Mechanically ventilated • Life expectancy < 6 mos • Active or recent RSV infection • Known immunoglobulin A deficiency • Known immunodeficiency • Previous reaction to blood products, albumin, or immune globulin (intravenous) [IGIV] • Treated with IGIV or any other immunoglobulin product within the previous 2 mos • Known renal impairment (creatinine > 2.5 mg/dL)	**Number** 510 randomized, 510 completed study **Sex** Placebo: 57.7% male (150/260) RSVIG IV: 57.2% male (143/250) **Mean age at enrollment (mos ± SE)** Placebo: 5.9 ± 0.27 RSVIG IV: 5.6 ± 0.29 **Mean gestational age (wks ± SE)** Placebo: 28.6 ± 0.21 RSVIG IV: 28.5 ± 0.20 **Comorbidities** BPD and prematurity, no other Comorbidities

Evidence Table 13. RSVIG IV vs. Placebo or Standard Care to Prevent RSV Bronchiolitis (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 260)** Placebo 1% albumin, administered by IV infusion **Group B (n = 250)** RSVIG IV 750 mL/kg, administered by IV infusion at a rate of 1.5 mL/kg/hr for the first 15 mins, then 3 mL/kg/hr from 15 - 30 mins, then 6 mL/kg/hr until the end of infusion Both placebo and RSVIG IV administered every 30 days from Nov Dec 1994 through April 1995 **Other treatment** Hospitalization, supplemental oxygen, ICU care, mechanical ventilation as indicated	**Outcomes** **Primary outcome** • Incidence of RSV hospitalizations (placebo vs. RSVIG IV) - 35/260 (13.5%) vs. 20/250 (8.0%) • Total number of RSV hospitalization days/100 children (placebo vs. RSVIG IV) - 129 vs. 60 • Total days of RSV hospitalization requiring supplemental oxygen/100 children (placebo vs. RSVIG IV) - 85 days vs. 34 days • Hospital days/100 children on which LRI score ≥ 3 (placebo vs. RSVIG IV) - 106 vs. 49 • ICU care for RSV (placebo vs. RSVIG IV) - 12/260 (4.6%) vs. 8/250 (3.2%) • Mechanical ventilation (placebo vs. RSVIG IV) - 5/260 vs. 5/250 • Incidence of overall respiratory hospitalizations (placebo vs. RSVIG IV) - 69 (27%) vs. 41 (16%) • Total number of respiratory hospital days/100 children (placebo vs. RSVIG IV) - 317 vs. 170 **Secondary outcomes** • Ribavirin use (placebo vs. RSVIG IV) - 10/35 (29%) vs. 7/20 (35%)	**Significant differences between study groups** • Yes (P = 0.047) • Yes (P = 0.045) • Yes (P = 0.007) • Yes (P = 0.049) • No (P value NR) • No (P value NR) • Yes (P = 0.005) • Yes (P = 0.005) • No (P = 0.62)	**Quality** Excellent **Significant differences at baseline** None **Other comments** 94% in placebo and 95% in RSVIG IV group completed protocol

Evidence Table 13. RSVIG IV vs. Placebo or Standard Care to Prevent RSV Bronchiolitis (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author The PREVENT Study Group, 1997[89] (continued)			

Evidence Table 13. RSVIG IV vs. Placebo or Standard Care to Prevent RSV Bronchiolitis (continued)

Intervention	Outcome		Quality
(continued)	**Subgroup analysis** • Prematurity - ≤ 6 mo at entry - ≤ 3 mo at entry • BPD • Age - ≤ 6 mo at entry • Weight ≥ or < 4.3 kg	• Trend toward fewer hospitalizations in all subgroup analyses for patients receiving RSVIG IV with reductions in hospitalizations ranging from 17% to 58%	
	Adverse events • Fever (1 in placebo, 2 in RSVIG IV) • Rash (1 in placebo) • Erythema multiforme (1 in placebo) • Respiratory distress (2 in RSVIG IV) • Acrocyanosis (2 in RSVIG IV) • Agitation and tachypnea (1 in RSVIG IV) • Decreased O_2 saturation (1 in RSVIG IV) • Death due to complications of prematurity and/or underlying chronic illness unrelated to study assignment • Adverse events judged potentially related to study drug as a reason for incomplete or prolonged infusion (1% in placebo vs. 3.2% in RSVIG IV)		

Evidence Table 14. Monoclonal Antibody for Prophylaxis of RSV Bronchiolitis

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author The IMpact – RSV Study Group 1998[91] **Setting** United States, United Kingdom, Canada, Inpatient and Outpatient **Followup** • Long-term – 150 days **Study design** RCT-P (2:1 randomization) **Length of enrollment** 1996 - 1997 RSV seasons **Masking** Double-blind	To evaluate the safety and effectiveness of monthly administration of palivizumab as prophylaxis for serious RSV illness in high-risk children	**Inclusion criteria** • ≤ 35 wks gestation and ≤ 6 mos old *or* • ≤ 24 mos old and had a clinical diagnosis of BPD requiring ongoing medical treatment (i.e. supplemental oxygen, steroids, bronchodilators, or diuretics within the past 6 mos **Exclusion criteria** • Hospitalization at the time of entry that was anticipated to last more than 30 days • Mechanical ventilation at the time of entry • Life expectancy less than 6 months • Active or recent RSV infection • Known hepatic or renal dysfunction, seizure disorder, immunodeficiency, allergy to 1gG products • Receipt of RSV immune globulin within past 3 months • Previous receipt of palivizumab, other monoclonal antibodies, RSV vaccines, or other investigational agents • Congenital heart disease, except children with patent ductus arteriosus or a septal defect that was uncomplicated and homodynamically insignificant	**Number** 1502 randomized, 1486 completed followup **Sex** Placebo: 56.8% male (284/500) Palivizumab: 56.9% male (570/1002) **Mean age at enrollment in mos ± SE** Placebo: 6.0 ± 0.21 Palivizumab: 5.7 ± 0.15 **Mean gestational age in wks ± SE** Placebo: 29 ± 0.14 Palivizumab: 29 ± 0.10 **Comorbidities** None other than prematurity and BPD

Evidence Table 14. Monoclonal Antibody for Prophylaxis of RSV Bronchiolitis (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 500)** Placebo 0.02 % Tween - 80 added to sterile water, IM every 30 days for a total 5 days, identical in appearance to palivizumab **Group B (n = 1002)** Palivizumab 15 mg/kg IM every 30 days for a total of 5 doses (final concentration of palivizumab = 100 mg/mL) **Other treatment** Hospitalization, oxygen supplementation, ICU care and mechanical ventilation as needed	**Outcomes** **Primary outcome** • Incidence of RSV hospitalizations (placebo vs. palivizumab) – 53/500 (10.6%) vs. 48/1002 (4.8%) **Secondary outcomes** • Total number of RSV hospitalization days/100 children (placebo vs. palivizumab) – 62.6 days vs. 36.4 days • Total days of RSV hospitalization requiring supplemental oxygen/100 children (placebo vs. palivizumab) – 50.6 days vs. 30.3 days • Hospital days/100 children on which LRI score ≥ 3 (placebo vs. palivizumab) – 47.4 vs. 29.6 • Incidence of ICU care for RSV (placebo vs. palivizumab) – 3% vs. 1.3% • Total days ICU care (placebo vs. palivizumab) – 12.7 vs. 13.3 • Incidence of mechanical ventilation (placebo vs. palivizumab) – 0.2% vs. 0.7% • Total days of mechanical ventilation (placebo vs. palivizumab) – 1.7 vs. 8.4 • Incidence of respiratory hospitalizations unrelated to RSV (placebo vs. palivizumab) – 14% vs. 13% • % children with at least 1 episode of otitis media – 40% vs. 42%	**Significant differences between study groups** • Yes ($P < 0.001$) • Yes ($P < 0.001$) • Yes ($P < 0.001$) • Yes ($P < 0.001$) • Yes ($P = 0.026$) • Yes ($P = 0.023$) • No ($P = 0.28$) • No ($P = 0.21$) • No ($P = 0.470$) • No ($P = 0.505$)	**Quality** Excellent **Significant differences at baseline** None **Other comments** None

Evidence Table 14. Monoclonal Antibody for Prophylaxis of RSV Bronchiolitis (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author The IMpact – RSV Study Group 1998[91] (continued)			

Evidence Table 14. Monoclonal Antibody for Prophylaxis of RSV Bronchiolitis (continued)

Intervention	Outcome		Quality
	Subgroup analysis		
	• Incidence of RSV hospitalizations by weight	• Yes	
	– > 5 kg	– (*P* 0.014)	
	– ≤ 5 kg	– (*P* = 0.001)	
	• Incidence of RSV hospitalizations by primary inclusion populations	• Yes	
	– Prematurity (no BPD)	– (*P* 0.001)	
	– BPD	– (*P* = 0.038)	
	• Incidence of RSV hospitalizations by length of gestation	• Yes	
	– <32 wks	– (*P* 0.003)	
	– 32 - 35 wks	– (*P* = 0.002)	
	Adverse events		
	• Fever	• No	
	• Nervousness	• No	
	• Injection site reaction	• No	
	• Diarrhea	• No	
	• Rash	• No	
	• Upper respiratory infection	• No	
	• Liver function abnormalities	• No	
	• Vomiting	• No	
	• Cough	• No	
	• Rhinitis	• No	
	• Death unrelated to study drug (5 in placebo group, 4 in palivizumab group)	• NR	

Evidence Table 14. Monoclonal Antibody for Prophylaxis of RSV Bronchiolitis (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Meissner et al., 1999[92] **Setting** Unspecified, Multi-center **Followup** • Acute • Short term - 8 wk followup **Study design** RCT-C **Length of enrollment** 1995 - 1996 RSV season **Masking** Double-blind	To evaluate the safety and pharmacokinetics of single and repeat in specified intramuscular doses of a humanized monoclonal antibody against RSV in a pediatric population at risk for severe RSV disease	**Inclusion criteria** • Born prematurely (= 35 wks), chronological age = 6 months *or* • Less than 37 months of age and history of BPD • Life expectancy of at least 6 mos **Exclusion criteria** • Known preexisting heart, liver, or renal disease • Recognized immune system abnormality • Severe respiratory illness requiring assisted ventilation • Previous gamma globulin infusion	**Number** 43 randomized, 42 completed study **Sex** 0.25 mg/kg SB209763: 38% male (3/8) 1.25 mg/kg SB209763: 45% male (5/11) 5.0 mg/kg SB209763: 27% male (3/11) 10.0 mg/kg SB209763: 77% male (10/13) **Mean age at enrollment in months (range)** 0.25 mg/kg SB209763: 6.0 (4 - 11) 1.25 mg/kg SB209763: 9.8 (0.75 - 30) 5.0 mg/kg SB209763: 9.8 (0.25 - 33) 10.0 mg/kg SB209763: 5.4 (0.75 - 13) **Mean gestational age** NR **Comorbidities** Prematurity:11 BPD plus prematurity:15 BPD alone:17

Evidence Table 14. Monoclonal Antibody for Prophylaxis of RSV Bronchiolitis (continued)

Intervention	Outcome		Quality
Intervention	**Outcomes**	**Significant differences between study groups**	**Quality**
Group A (n = 8) 0.25 mg/kg SB209763 (n = 6) IM into single thigh muscle, reconstituted with sterile water to a concentration of 45 mg/ml Placebo (n = 2) Similar volume as intervention After 8 wks, placebo group crossed over to SB209763 and both groups received 2nd IM dose	**Primary clinical outcome** • RSV infection episodes/dosage (10 mg/kg SB209763 vs. placebo) - 1/22 vs. 2/10 • RSV infection episodes/dosage (5 mg/kg SB209763 vs. placebo) - 2/19 vs. 2/10 • RSV infection episodes/dosage (1.25 mg/kg SB209763 vs. placebo) - 2/20 vs. 2/10 • RSV infection episodes/dosage (0.25 mg/kg SB209763 vs. placebo) - 2/14 vs. 2/10 **Adverse events** • Safety (SB209763 vs. placebo) - 37 events in 10 patients receiving placebo - 192 events in 35 patients receiving SB209763 • 4 events considered related to study - 3 episodes of mild to moderate purpura - 1 episode of thrombocytosis	• No (P = 0.20) • No (P = 0.49) • No (P = 0.46) • No (P = 0.72)	Good **Significant differences at baseline** None **Other comments** • High dose group mostly male • Primary purpose of study was safety and pharmaco - dynamics, not efficacy
Group B (n = 11) 1.25 mg/kg SB209763 (n = 9) IM into single thigh muscle Placebo (n = 2) Similar volume as intervention Dosing schedule: Similar crossover as Group A (placebo to intervention at 8 wks, second dose IM)			
Group C (n = 12) 5.0 mg/kg SB209763 (n = 8) Divided into 2 doses, IM into each thigh muscle Placebo (n = 3) Similar volume as intervention			

Evidence Table 14. Monoclonal Antibody for Prophylaxis of RSV Bronchiolitis (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Meissner et al., 1999[92] (continued)			

Evidence Table 14. Monoclonal Antibody for Prophylaxis of RSV Bronchiolitis (continued)

Intervention	Outcome	Quality
Dosing schedule: Similar crossover as Group A (placebo to intervention at 8 wks, second dose IM) **Group D (n = 13)** 10.0 mg/kg SB209763 (n = 10) Divided into 2 doses, IM into each thigh muscle Placebo (n = 3) Similar volume as intervention Dosing schedule: Similar crossover as Group A (placebo to intervention at 8 wks, second dose IM) Max volume at highest dose 0.22ml/kg **Other treatment** NR		

Evidence Table 15. Vaccines to Prevent RSV Bronchiolitis

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Groothuis et al., 1998[93] **Setting** United States, Outpatient at baseline, weekly telephone followup, Outpatient at 1 mo. and 6 mo. after intervention **Followup** • Short term: 1 mo. after intervention • Long-term: 6 mo. after intervention and the subsequent RSV season **Study design** RCT non-placebo **Length of enrollment** Oct and Nov 1991 **Masking** Double-blind	To assess the safety, immunogenicity, and efficacy of an improved purified F protein vaccine (PFP-2) in a high-risk population of young seropositive children with BPD	**Inclusion criteria** • < 12 months of age with bronchopulmonary dysplasia • Proven RSV infections in a previous respiratory season • Influenza vaccination in previous year • Outpatients in Neonatal High Risk Follow Up Program at Children's Hospital, Denver **Exclusion criteria** None listed	**Number** 21 randomized, 21 completed study **Sex** NR **Age at enrollment in months** PFP-2: 32.2 Placebo: 30.0 **Mean gestational age** NR **Comorbidities** NR

Evidence Table 15. Vaccines to Prevent RSV Bronchiolitis (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 10)** PFP-2 vaccine 0.5 ml IM **Group B (n = 11)** Trivalent influenza vaccine 0.5 ml IM **Other treatment** All patients received unblinded dose of trivalent influenza vaccine 4-6 wks after study vaccine	**Outcomes** **Primary outcome** • RSV infections in subsequent season (PFP-2 vs. Influenza vaccine) - 1/10 vs. 6/11 **Secondary outcomes** • Mean F protein antibody before vaccination PFP-2 vs. Influenza vaccine) • Mean F protein antibody 1 month after vaccination (PFP-2 vs. Influenza vaccine) • Mean F protein antibody 6 month after vaccination (PFP-2 vs. Influenza vaccine) • Mean neutralizing antibody before vaccination (PFP-2 vs. Influenza vaccine) • Mean neutralizing antibody 1 month after vaccination (PFP-2 vs. Influenza vaccine) • Mean neutralizing antibody 6 month after vaccination (PFP-2 vs. Influenza vaccine) **Subgroup analysis** None **Adverse events** • Irritability (2 PFP - 2 patients, 2 influenza vaccine) • Drowsiness (1 PFP - 2 patient) • PIain and tenderness (1 PFP - 2 patients, 1 influenza vaccine) • Redness (1 PFP - 2 patient)	**Significant differences between study groups** • No (P = 0.06) • No (P = 0.22) • Yes (P 0.0001) • Yes (P = 0.002) • No (P = 0.78) • Yes (P = 0.006) • Yes (P = 0.009)	**Quality** Good **Significant differences at baseline** None **Other comments**

Evidence Table 15. Vaccines to Prevent RSV Bronchiolitis (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Piedra et al., 1996[94] **Setting** United States, Outpatient at baseline, telephone interview at followup **Followup** • Short term - length of the RSV season **Study design** RCT-P **Length of enrollment** 1993 to 1994 RSV season **Masking** Double-blind	To determine the safety and immunogenicity of the PFP-2 vaccine in children with CF who are at high risk of LRTI with RSV infection	**Inclusion criteria** • Diagnosis of CF based on two of following criteria: - sweat chloride > 60 meq/L - genetic testing demonstrating homozygosity for the delta F508 allele - clinical features consistent with cystic fibrosis **Exclusion criteria** • Pre-vaccine RSV serum neutralizing antibody filter of < 1:4 • History of epilepsy • Recent history of febrile seizure	**Number** 34 completed study **Sex** PFP-2: 59% male Saline: 65% male **Mean age at enrollment (yr ± SD)** PFP-2: 4.5 ± 1.6 Saline: 5.8 ± 1.6 **Mean gestational age** NR **Comorbidities** All enrollees had CF

Evidence Table 15. Vaccines to Prevent RSV Bronchiolitis (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 17)** PFP-2 IM 50 µg of PFP-2 composed of F glycoprotein of the A2 strain of RSV compounded with alum, 1 dose **Group B (n = 17)** IM Saline 0.5 ml **Other treatment** Antibiotics	**Outcomes**	**Significant differences between study groups**	**Quality** Good **Significant differences at baseline** PFP-2 group significantly taller, older, and had lower triceps fat fold thickness **Other comments** None
	Primary outcomes		
	• Development of RSV ± SD (PFP-2 vs. Saline)	• No (P = 0.73)	
	- 7/17 (41%) vs. 9/17 (53%)		
	• Total days of illness of RSV infection ± SD (PFP-2 vs. Saline)	• NR	
	- 45 vs. 119		
	• Hospitalization	• No (P = 0.087)	
	- 1/17 vs. 5/17		
	• No. with = 1 ALRTI (acute lower respiratory tract infection)	• Yes (P = 0.024)	
	- 9/17 vs. 15/17		
	• Mean no. of AURTI/subject (acute upper respiratory tract infection) ± SD (PFP-2 vs. Saline)	• No (P = 0.35)	
	- 2.0 ± 1.5 vs. 2.5 ± 1.6		
	• Mean no. of ALRTI/subject ± SD (PFP-2 vs. Saline)	• Yes (P = 0.005)	
	- 0.8 ± 0.9 vs. 2.1 ± 1.4		
	• Mean no. of antibiotic courses/subject ± SD (PFP-2 vs. Saline)	• Yes (P < 0.001)	
	- 2.2 ± 1.3 vs. 4.5 ± 1.5		
	• Mean no. of days ill/subject	• Yes (P < 0.001)	
	- 30.5 ± 16.1 vs. 67 ± 25.8		
	Subgroup analysis		
	• RSV exposure status	• No significant differences	
	Adverse events		
	• Weakness/ache/nausea	• No significant differences	
	• Any systematic symptoms (PFP-2 vs. saline)	• No significant differences	
	– 5 vs. 6		
	• Any local reaction (PFP2 vs. saline)	• No significant differences	
	– 8 vs. 4		

Evidence Table 15. Vaccines to Prevent RSV Bronchiolitis (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Piedra et al., 1998[95] **Setting** United States, Outpatient **Followup** • Acute • Short term - weekly • Long-term - 1 yr after initial vaccine **Length of enrollment** 1993 - 1995 **Study design** Open - label followup of original study that was RCT-P, all patients received followup vaccine **Masking** Not clear if parents/ caregivers were unblinded in this study	To determine the safety and immunogenicity of yearly sequential administration of the PFP-2 vaccine in children with cystic fibrosis Note: This is a followup of Piedra et al. 1996.	**Inclusion criteria** Diagnosis of CF as previously described in Piedra et al.[94] on two of following criteria: - sweat chloride > 60 meq/l - genetic testing demonstrating homozygosity for the delta F508 allele - clinical features consistent with cystic fibrosis **Exclusion criteria** Details NR in this study. Piedra et al. 1996[94] states • Pre - vaccine RSV serum neutralizing antibody filter of < 1:4 • History of epilepsy • Recent history of febrile seizure	**Number** 34 in initial study, 29 completed this 2nd study **Sex** PFP/PFP: 57% male (8/14) Saline/PFP: 60% male (9/15) **Mean age at enrollment in years ± SD** PFP/PFP: 5.6 ± 1.8 Saline/PFP: 6.8 ± 1.5 **Mean gestational age** NR **Comorbidities** CF, mild lung disease

Evidence Table 15. Vaccines to Prevent RSV Bronchiolitis (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 14)** PFP/PFP IM 50 µg of PFP-2 in 0.5 ml in Fall 1993 and Fall 1994 **Group B (n = 15)** Saline/PFP Saline placebo in Fall 1993 (details not reported) PFP/PFP: IM 50 µg of PFP-2 in 0.5 ml in Fall 1994 **Other treatment** Antibiotics	**Outcomes** **Primary outcome** • No. with = 1 ALRTI - 9/13 vs. 15/15 • Mean no. of illnesses/subject ± SD (PFP/PFP vs. Saline/PFP) - 3.2 ± 1.5 vs. 4.1 ± 1.2 • Mean no. of AURTI/subject ± SD (PFP/PFP vs. Saline/PFP) - 2.1 ± 1.3 vs. 2.1 ± 1.2 • Mean no. of ALRTI/subject ± SD (PFP/PFP vs. Saline/PFP) - 1.2 ± 1.0 vs. 2.1 ± 0.5 • Mean no. of antibiotic courses/subject ± SD (PFP/PFP vs. Saline/PFP) - 2.8 ± 2.5 vs. 4.4 ±. 2.0 • Mean no. of days ill/subject - 36. ± 19.4 vs. 64.8 ± 27.0 **Subgroup analysis** • Confirmed RSV infection - No. with = 1 ALRTI - Mean no. of illnesses/subject ± SD (PFP/PFP vs. Saline/PFP) - Mean no. of AURTI/subject ± SD (PFP/PFP vs. Saline/PFP) - Mean no. of ALRTI/subject ± SD (PFP/PFP vs. Saline/PFP) - Mean no. of antibiotic courses/subject ± SD (PFP/PFP vs. Saline/PFP) - Mean no. of days ill/subject	**Significant differences between study groups** • Yes (P = 0.035) • No (P = 0.098) • No (P = 0.98) • Yes (P = 0.004) • No (P = 0.077) • Yes (P = 0.001) • Some outcomes significantly different between groups	**Quality** Fair **Significant differences at baseline** • Saline/PFP taller (P value NR) and older (P = .06) • Saline/PFP children more likely to attend daycare/ school (P = 0.08) **Other comments** • Significant effects may be explained by lower incidence of RSV exposure in PFP/PFP group due to lower daycare attendance • N for subgroup analysis very low

Evidence Table 15. Vaccines to Prevent RSV Bronchiolitis (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Piedra et al.1998[95] (continued)			

Evidence Table 15. Vaccines to Prevent RSV Bronchiolitis (continued)

Intervention	Outcome		Quality
	Adverse events • 1 death unrelated to vaccination or RSV infection (1 PFP/PFP pt.) • Weakness/ache/nausea • Fever • Headache • Any systemic reaction – 7/14 vs. 7/15 • Tenderness at vaccine site • Edema at vaccine site • Red at vaccine site • Any local reaction – 4/14 vs. 5/15	• No significant differences between groups	